# FORMULATION AND EVALUATION OF EXTENDED RELEASE METOPROLOL SUCCINATE MATRIX TABLETS

**Dissertation submitted to**

**THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32**

***In partial fulfillment for the award of the degree of***

**MASTER OF PHARMACY**

**IN**

**PHARMACEUTICS**

***Submitted by***

**Register No: 26111013**

**UNDER THE GUIDANCE OF**

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# CERTIFICATE

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# To whomsoever it may concern

This is to certify that Ms.Y.RAMYA a student of M-Pharmacy Final year C.L.BAID METHA COLLEGE OF PHARMACY has completed her project work in our company during 08-07-2012 to 01-01-2013.

Project Title: Formulation and evaluation of extended release ***METOPROLOL SUCCINATE*** matrix tablets

During her Project work here, she was sincere and hard working. We wish her all success in her future endeavors.

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# DECLARATION

I hereby declare that the thesis entitled "**FORMULATION AND EVALUATION OF EXTENDED RELEASE METOPROLOL SUCCINATE MATRIX TABLETS**" has been originally carried out by me under the supervision and guidance of **Mr.Srinivas Reddy** M.Pharm (Industrial guide) and **Dr.Grace Rathnam**. M.Pharm.,Ph.D, Head of the department,(Institutional guide). Department of Pharmaceuicts, C.L. Baid Metha College of Pharmacy, Chennai-600 097 , during the academic year 2012-2013

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Last but not the least I wish to express my deepest sense to respect and love to my parents for their constant support and encouragement throughout.

**(Reg.No: 26111013)**

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **API** | Active pharmaceutical ingredient |
| **BCS** | Bio pharmaceutics classification system |
| **BSS** | British Sieve Specification |
| **CR** | Controlled release |
| **DR** | Delayed release |
| **ER** | Extended release |
| **EG** | Extra granular |
| **FDA** | Food and drug administration |
| **GIT** | Gastro intestinal tract |
| **HME** | Hot melt extrusion |
| **IR** | Immediate release |
| **LOD** | Limit of drying |
| **MEC** | Minimum effective concentration |
| **MTC** | Maximum toxic concentration |
| **NMT** | Not more than |
| **RH** | Relative humidity |
| **RSD** | Relative standard deviation |
| **WHO** | World health organization |

**DRUGS**

| | |
|---|---|
| **HPMC** | Hydroxy propyl methyl cellulose |
| **HCL** | Hydrochloride |

| | |
|---|---|
| **MCC** | Micro crystalline cellulose |

## INSTRUMENTS

| | |
|---|---|
| **FBC** | Fluid bed coating |
| **FTIR** | Fourier transform infrared spectroscopy |
| **HPLC** | High performance liquid chromatography |
| **KF** | Karl fischer titration |
| **RMG** | Rapid mixer granulator |
| **UV** | Ultra violet |

## NOMENCLATURE

| | |
|---|---|
| **°C** | Degrees centigrade |
| **%** | Percentage |
| **Hrs** | Hours |
| **J/g** | Joule per gram |
| **Cal/g** | Calories per gram |
| **W/V** | Weight per volume |
| **w/w** | weight per weight |
| **λ** | wavelength |
| **rpm** | Revolution per minute |
| **Mpas** | Milli pascals |
| **CP** | Centipoise |
| **µm** | Micro meter |
| **µL** | Micro liters |
| **nm** | Nano meters |

| | |
|---|---|
| **cm** | Centimeters |
| **mm** | Milli meters |
| **ml** | Milli liters |
| **m/g** | Mass per gram |
| **mg** | Milli gram |
| **$g/cm^3$** | Gram per centimeter cube |
| **mg/kg** | milli gram per killo gram |

# CONTENTS

# INTRODUCTION

## 1.1 EXTENDED RELEASE DRUG THERAPY

For many decades treatment of acute diseases or chronic illnesses have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, liquids, aerosols and injectables. Even today these conventional dosage forms are the primary pharmaceutical vehicles commonly seen in the prescription and over the counter drug market. The oral conventional types of drug delivery systems are known to provide a prompt release of the drug. Therefore to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in a significant fluctuation in drug levels often with a sub-therapeutic and or toxic levels and wastage of drug. Recently several technical advancements have resulted in the development of new systems of drug delivery capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a tissue[1].

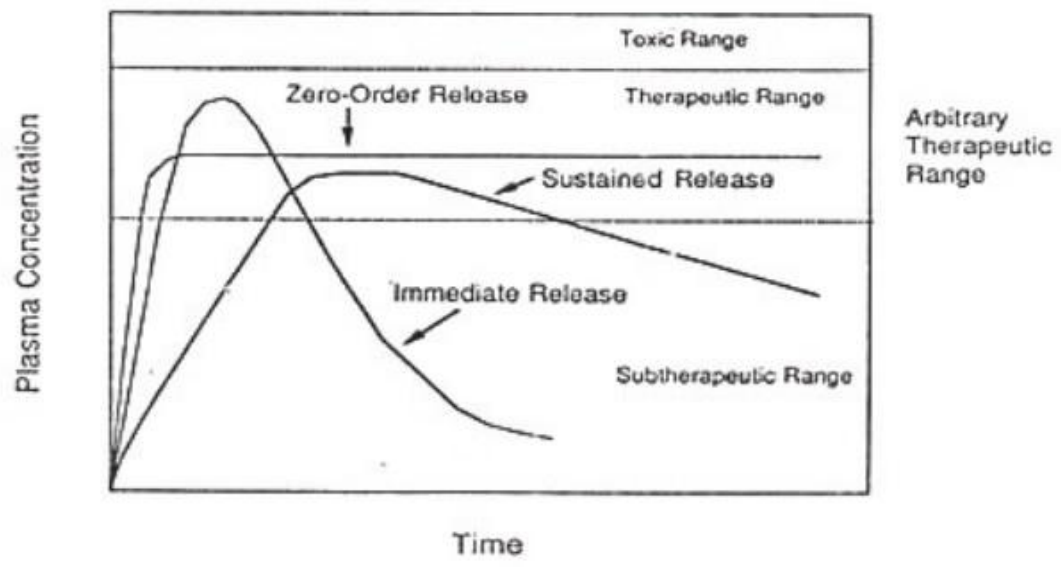

**Fig-1: plasma level versus time profile showing difference between controlled release, sustained release and release from conventional dosage form.**

The term controlled\extended release implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and a known mechanism of release. This means that the release of drug ingredient(s) from a controlled release drug delivery system proceeds at a rate that is not only predictable kinetically but also reproducible from one unit to another. In other words, the system attempts to control drug concentration in the target tissue.

The oral route of administration for extended release systems has received greater attention because of more flexibility in dosage form design. The design of oral extended release delivery systems is subjected to several interrelated variables of considerable importance such as type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.

***Extended release***[2]denotes that the system is able to provide some actual therapeutic control whether be it of temporal or spatial nature or both. In other words, the system attempts to provide a constant drug concentration in the target tissue. It is this nature of this system that makes it different from sustained release systems.

### 1.1.1 Advantages of extended release dosage form:[3]

- **Improved patient compliance** and convenience due to less frequent drug administration.
- **Reduction in fluctuation** in steady state levels and therefore, better control of disease condition and reduction intensity of local or systemic side effects.
- **Increased safety margin** of high potency drugs due to better control of plasma levels.
- **Maximum utilization of drug** enabling reduction in total amount of dose administered.

- **Reduction in health care costs** through improved therapy, shorter treatment period, less frequent dosing and reduction in personnel time to dispense, administer and monitor patients.
- **Sustained blood levels**; the size and frequency of dosing are determined by the pharmacokinetic and pharmacodynamic property of drug. The use of extended releaseproducts may maintain therapeutic concentration over prolonged period.
- **Attenuation of adverse effect**, the use of extended release products avoids the high initial blood concentration, which may cause many side effects like nausea, local irritation, haemodynamic changes etc.

### 1.1.2 Disadvantages of Extended release dosage form: [3]

- Toxicity due to dose dumping.
- Increased cost.
- Unpredictable and often poor *in vitro- in vivo* correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Local irritation or damage of epithelial lining (lodging of dosage forms).
- Need for additional patient education and counseling.
- Increased potential for first- pass clearance.

### 1.1.3 Ideal candidate for extended/controlled release drug delivery systems: [4-6]

The desired biopharmaceutical characteristics of drugs to be used in the development of per oral CR dosage forms are:

| | | |
|---|---|---|
| Molecular weight | : | <1000 Mg |
| Solubility | : | 0.1 Mcg/ ml |

$P^{ka}$ : >0.1% to 1% at pH 1 to 7.8

Apparent partition coefficient : 0.5 to 2.0

General absorbability : From all GI segments

Stability : Stable in GI environment

Release should not be influenced by pH and enzymes.

Less protein binding

To evaluate whether a drug is viable candidate or not for the design of per oral CR formulation, one must consider the following pharmacokinetic parameters of the drug.

Elimination half-life : Preferably between 0.5& 8 hours

Total body clearance : Should not be dose dependent

Elimination – rate constant : Required for the design

Absolute bioavailability : Should be 75% or more

Absorption rate : Must be greater than release rate

**Therapeutic concentration :**

The lower the $C_{ss}^{av}$ and the smaller the $V_d$ the lesser is the amount required.

**Apparent volume of distribution ($V_d$):**

The larger the $V_d$ and MEC, the larger will be the dose size required. The maximum dose to be incorporated in to a per oral CR formulations is about 500 mg. The smaller the $V_d$, the easier is incorporation of drug in to dosage form.

**Minimum toxic concentration (MTC):**

MTC and MEC, the further apart of these t values are, the safer the dosage and also suitable for drugs with very short $t^{1/2}$

## 1.1.4 Factors influencing oral extended release dosage design:

### 1.1.4.1 Biological Factors:

**Biological Half Life:**

The usual goal of an oral extended –release product is to maintain therapeutic blood levels over an extended period. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by half-life $t^{1/2}$. Each drug has its own characteristic elimination rate, which is the sum of all elimination process, including metabolism, urinary excretion and all other process that permanently remove drug from the bloodstream.

Therapeutic compounds with short half-lives are excellent candidates for sustained release preparation, since this can reduce dosing frequency. However this is limited. In general, drugs with half-lives shorter than 2hrs, such as furosemide or levodopa[7]are poor candidates for sustained release preparations. Compounds with long half-lives, more than 8hrs are also generally not used in sustained release forms, since their effect is already sustained. dig toxin, wayfaring, phenytoin[8] are some examples.

**Absorption**

The characteristics of absorption of a drug can greatly affect its suitability as a extended-release product. Since the purpose of forming an extended-release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs and devices in the absorptive areas of GI tract is about 8-12hrs, the maximum half-life for absorption should be approximately 3-4hrs; otherwise, the device will pass out of the potential regions before absorption is complete[9]. If a drug

is absorbed by active transport or transport is limited to a specific region of the intestine, sustained release preparations may be disadvantageous to absorption.

Absorption of ferrous sulphate is maximal in the upper jejunum and duodenum and sustained-release mechanisms that do not release drug before passing out of this region are not beneficial[10]. It is observed that co administration of food results in a sustaining effect[11] although administration of food can create highly variable effects, there have been methods devised to circumvent this problem. One such attempt is to formulate low-density pellets, capsules[12]tablets[13]. These float on the top of the gastric juice, delaying their transfer out of the stomach[14]. The increase in gastric retention results in higher blood levels for P-amino benzoic acid, a drug with a limited GI absorption range[15], but the drugs that have widespread absorption in the intestinal system would likely not benefit from an increase in emptying time[16] .

Another approach is that of bio adhesive materials. The principle is to administer a device with adhesive polymers having an affinity for the gastric surface, most probably the mucin coat[17]. Bio adhesives have demonstrated utility in the mouth, eye and vagina.

**Metabolism**

Drugs that are significantly metabolized before absorption, either in the lumen or the tissue of the intestine can show decreased bioavailability from slower releasing dosage forms. For example, aloprenolol was more extensively metabolized in the intestinal wall when given as a sustained-release preparation[18].High concentrations of dopa-decarboxylase in the intestinal wall will result in a similar effect for levodopa[19]. If levodopa is formulated in a dosage form with a drug compound that can inhibit the dopa-carboxylase enzyme, the amount of levodopa available for absorption increases and can sustain its therapeutic effects.

Formulation of these enzymatically susceptible compounds as prodrugs is another viable solution.

## 1.1.4.2 Physicochemical Factors Influencing Oral Extended-Release Dosage Form Design

### Dose size

For orally administered system, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0 gm is considered maximal for the conventional dosage form[20]. This also holds for sustained-release dosage form, those compounds that require a large dosing size can sometimes can be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amounts of drug with narrow therapeutic range.

### Ionization, pKa and Aqueous Solubility

Most drugs are weak acids or bases. Since the unchanged form of drug preferentially permeates across lipid membrane, the drug in an unchanged form is advantageous for drug permeation. Consider a drug for which the highest solubility is in the stomach and is unchanged in the intestine. For conventional dosage forms, the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of intestine. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form, meaning that the solubility of the drug may change several orders of magnitude during its release.

Compounds with very low solubility (<0.01 mg/ ml) are inherently sustained. The drugs that are limited in absorption by the dissolution rate are digoxin[21], griseofulvin[22]and salicylamide[23]. The lower limit has been reported to be 0.1 mg/ ml[24].

### Partition coefficient

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect these membranes are lipid in nature therefore, the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Compounds with a relatively high partition coefficient are predominantly lipid soluble and consequently, have very low aqueous solubility. Phenothiazine's are representative of this type of compound[25]

**Stability**

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems prolong delivery over the entire course of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drug is delivered in the small intestine and hence it is subject to degradation. Propantheline[26] and probanthine[26] are representative examples of such drugs.

## Unsuitable candidates for extended-Release dosage forms[28]:

Short elimination biological half-life

E.g. Penicillin G, Furosemide

Long elimination biological half life (>12hrs)

E.g. Diazepam, Phenytoin

Narrow therapeutic index

E.g.Phenobarbital, Digitoxin.

Not effectively absorbed in the lower intestine.

E.g. Riboflavin, Ferrous salts.

No clear advantage for sustained release formulation

E.g.Griseofulvin.

Large doses (>1g)

E.g.Sulphonamides.

### 1.1.5 Methods to retard the drug release

Combining the classification methodology used by Carmella et al and controlled release products can be classified as follows:

- Reservoir systems including

  Enteric coated tablets, capsules, coated granules and microcapsules.

- Osmotic systems.
- Ion-exchange resins.
- Matrix systems.

### 1.1.6 Mechanism of drug release in extended release systems

The different mechanisms of drug release in controlled release systems are:

1. Dissolution-controlled release

2. Osmotically controlled release

3. Diffusion-controlled release

4. Erosion controlled release

5. Miscellaneous controlled release

**1. Dissolution-controlled release:**

In extended-release formulations employing dissolution as the rate-limiting step, drug release is controlled by dissolution of a polymer. Individual particles or granules containing a drug can be unifor mly dispersed in the matrix or coated with varying thicknesses of coating material resulting in dissolution and release of the drug over extended periods of time. If the dissolution process is assumed to be

diffusion-layer controlled, in which the rate of diffusion from the solid surface to the bulk solution is rate-limiting, the flux is the product of the diffusion coefficient and the concentration gradient from the solid surface to the bulk solution side. Flux can also be defined as the flow rate of material through a unit area. With encapsulated dissolution control, the drug may be coated with slowly dissolving polymeric materials. Once the polymeric membrane has dissolved, the entire drug inside the membrane is immediately available for dissolution and absorption. Thus, drug release can be controlled by adjusting the thickness and the dissolution rate of the polymeric membrane.

**2. Osmotically Controlled Systems**

In addition to the mechanism of solution diffusion, drug release from a membrane-reservoir device can also take place through a membrane via an osmotic pumping mechanism. In this case, a semi permeable membrane, such as cellulose acetate, is utilized to regulate osmotic permeation of water. With constant reservoir volume, this type of device delivers a volume of drug solution equal to the volume of osmotic water uptake within any given time interval. The rate of osmotic water influx, and therefore the rate of drug delivery by the system, will be constant as long as a constant thermodynamic activity gradient is maintained across the membrane. Such an osmotic delivery system is capable of providing not only a prolonged zero-order release, but also a delivery rate much higher than that achievable by the solution-diffusion mechanism. Osmotic ally controlled release is also applicable to drugs with a wide range of molecular weight and chemical composition, which are normally difficult to deliver by the solution-diffusion mechanism.

**3. Diffusion Controlled Systems**

The most commonly used type of membrane material in drug delivery systems is homogeneous films of amorphous and semi crystalline polymers above their glass transition temperatures. Drug transport occurs by dissolution in the membrane at one interface, followed by diffusion down a concentration gradient across the membrane and, finally, release from the second interface into the external medium. The rate of drug permeation through solution-diffusion membranes is

directly proportional to the product of the drug-diffusion coefficient in the polymer and the polymer/solution partition coefficient. In diffusion-controlled release systems, the transport of solute through the polymer is achieved by molecular diffusion due to concentration gradients. Depending on the molecular structure of the polymer, these systems may be classified as porous or nonporous. Porous controlled-release systems contain pores of large enough size so that diffusion of the solute is accomplished through water, which has filled the pores of the polymer.

In **reservoir (membrane) systems**, the bioactive agent is usually enclosed at relatively high concentrations between two semi permeable membranes and placed in contact with a dissolution medium (water or other biological fluid).

In **matrix (monolithic) systems**, the bioactive agent is incorporated in the polymer phase either in dissolved or in dispersed form. Therefore, the solubility of the solute in the polymer becomes a controlling factor in the mathematical modeling of these systems.

**4. Erosion controlled release**

Chemically controlled systems include all polymeric formulations in which solute diffusion is controlled by a chemical reaction, such as the dissolution of the polymer matrix or cleavage of the drug from a polymer backbone. In most chemically controlled systems, solute release is controlled by the geometric shape of the device. Depending on the type of degradation reaction, these systems may be classified as **chemically degradable** (e.g., by hydrolysis) or **biodegradable** (e.g., by enzymatic reaction) controlled-release systems.

**5. Miscellaneous forms of controlled release**

Ion-exchange resins

Altered density: Drug-coated micro pellets

pH-independent formulations

Barrier coating

Embedment in slowly eroding matrix Embedment in plastic matrix Repeat action

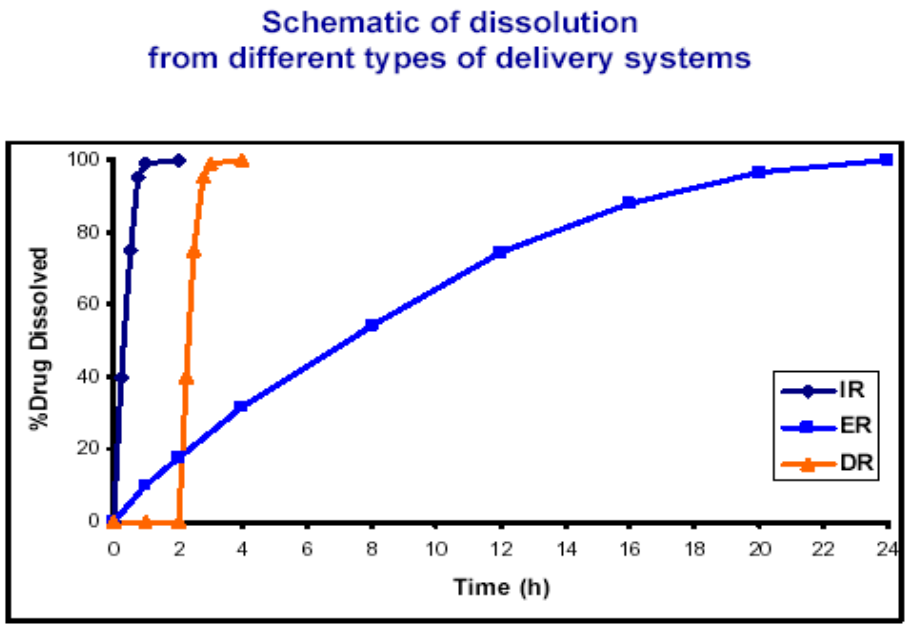


**Fig. 2: Schematic representation of dissolution from different types of delivery systems**

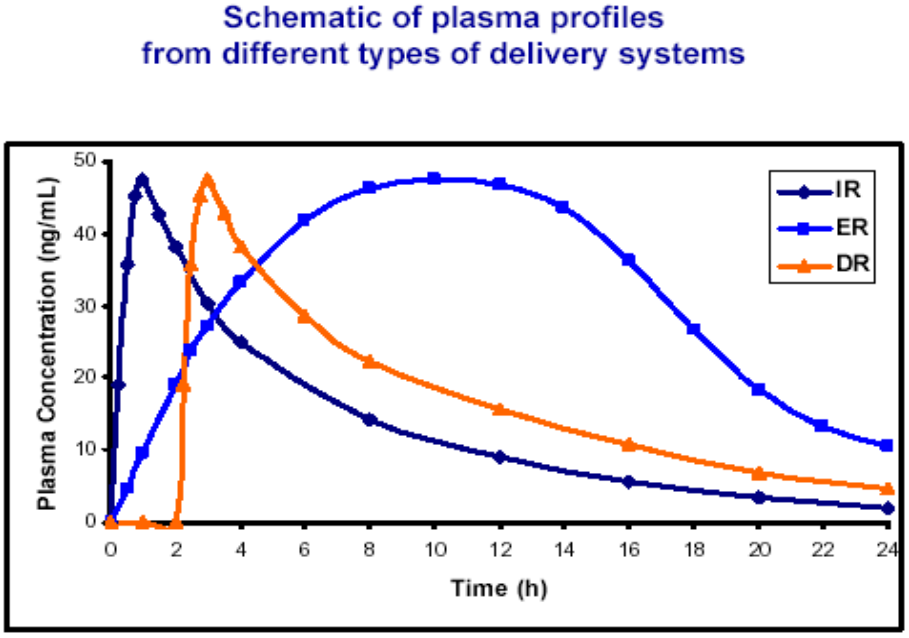


**Fig.3 : Schematic representation of plasma profiles from different types of delivery systems**

**IR:**Immediate release, **ER**:Extended release, **DR**:Delayed release

**Table1. CLASSIFICATION OF ORAL CONTROLLED RELEASE SYSTEMS**:

| TYPE OF SYSTEM | RATE CONTROLLING MECHANISM |
|---|---|
| **Diffusion Controlled** | |
| • Reservoir system | Diffusion through a membrane |
| • Monolithic system | |
| **Water permeation controlled** | |
| • Osmotic systems | Osmotic transport of water through a semi permeable membrane |
| • Swelling systems | Water penetration into a glassy polymer |
| **Chemically Controlled** | |
| • Monolithic system | Either pure polymer erosion (surface erosion) or a combination of erosion and diffusion(bulk erosion) |
| • Pendent systems | Combination of hydrolysis of the pendent group and diffusion from the bulk polymer |
| • Ion exchange resins | Exchange of acidic or basic drugs with ions present on resins |
| **Regulated systems** | |
| • Magnetic, Ultrasound | External application of magnetic field or ultrasound device |
| • Chemical | Use of competitive desorption or enzyme substrate reactions. Rate control is built into the device. |

### 1.1.7 Regulatory considerations in extended release products[27]:

- The drug product meets the controlled release claims made for it.
- The bioavailability profile established for the drug product rules out the possibility of any dose dumping.
- The drug product's steady-state performance is equivalent to a currently marketed non-controlled release or controlled release drug product with the same active ingredient or therapeutic moiety, which has been subjected to an approved full new drug application.
- The drug product's formulation provides consistent pharmacokinetic performance between administrations.
- The reference standard for comparative studies should include one of the following
- A solution or suspension of the same active drug ingredient or therapeutic moiety.
- A currently marketed approved non-controlled release drug product containing the same active drug ingredient or therapeutic moiety.
- A currently marketed controlled release drug product subject to an approved full new drug application containing the same active drug ingredient or therapeutic moiety.

## 1.2 MATRIX FORMULATION: [27-29]

### 1.2.1 Definition:

Matrix formulations are defined as a drug or other active ingredient embedded in insoluble excipient in order to achieve release by a continuous leaching of the drug from the inert matrix core.

## 1.2.2 Classification:

Matrix systems can be divided into three types:

- Monolithic matrix tablets.
- Gel forming hydrophilic matrix tablets.
- Erodible (hydrophobic) matrix tablets.

### ➢ Inert monolithic matrix tablets:[28]

Probably the simplest method of obtaining sustained release of a drug from an oral dosage form is incorporation of a drug in an inert matrix. In this inert means non-interacting with the biological fluids. The main reason for its popularity is that drug release from plastic matrix tablets is independent on the state and condition of the digestive juices, which may show large inter- and intra-patient variability (pH, viscosity).

During its transit through the gastro-intestinal tract, the porous matrix tablet does not disintegrate like conventional tablets, but remains intact and the skeleton can be recovered in feces. The materials used in the preparation of these inert matrices are predominantly (insoluble) polymers and lipophilic compounds. The first polymers to be used for the preparation of matrix tablets were (semi) synthetic polymers such as polyethylene, polyvinyl chloride, polymethyl methacrylate, polystyrene, poly vinyl acetate, cellulose acetate and ethyl cellulose. The fat compounds used included carnauba wax, hydrogenated castor oil, and tristearin.

Major drawback of most of the inert polymeric matrix tablets were their inherent first order drug release characteristics, their poor direct compression characteristics and the problematic cleaning of agglomeration equipment used for the preparation of agglomerates with the required compression characteristics.

### Mechanism of release of inert monolithic matrix tablets:[29]

Release from inert matrix tablets occurs via a leaching mechanism. Drug particles dispersed in the polymer matrix dissolve in the penetrating gastro-

intestinal fluids and are released from the tablet by diffusion through the porous network of already existing pores and pores that are created by dissolution of the drug particles. At drug loadings exceeding approximately 10-15 volume %, a continuous structure connecting all drug particles exists (percolating drug network). At considerably lower loadings, a particular fraction of the drug may be completely surrounded by the polymer matrix (trapped fraction), which would result in incomplete release.

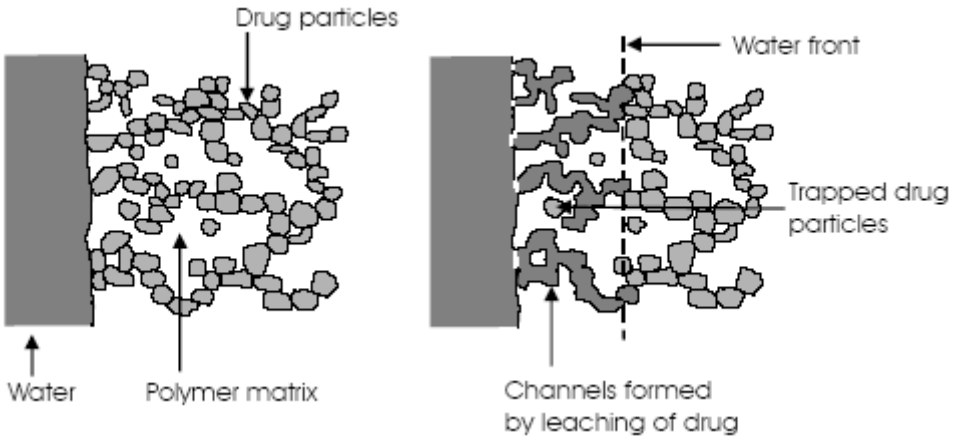


**Fig .4: Schematically representation of a leaching-based release mechanism.**

- **Solvent activated matrix tablets:**

The use of solvent activated matrix tablets as a method to obtain zero order release i.e. constant release rates over an extended period was first proposed by Hopfenberg. Solvent-activated drug delivery system is a collective term comprising those systems in which the interaction between polymer and water is responsible for achieving controlled release. The interaction with water may include plasticization, swelling, dissolution, erosion or degradation of the polymer. The two most important types of solvent activated matrix tablets are gel-forming hydrophilic matrix tablets and erodible (hydrophobic) matrix tablets.

- **Gel-forming hydrophilic matrix tablets:**

Gel-forming hydrophilic or swell able matrix systems are homogeneous or heterogeneous systems in which the drug is dispersed in a swell able hydrophilic polymer. These systems have been widely studied by researchers since they offer

the possibility to obtain a constant drug delivery over an extended period of time. Drug release is a function of the polymer characteristics.

Upon swallowing gel-forming hydrophilic matrix tablets, the hydrophilic polymer is plasticized by the aqueous gastro-intestinal due to which undergoes macromolecular chain relaxation and volume expansion. Consequently, upon penetration of the gastro-intestinal fluids into tablet, a sharp front can be distinguished which separates a dry, glassy core from a hydrated and rubbery gel layer. Release is governed by diffusion of the dissolved drug through the swollen gel layer and generally shows a burst effect, caused by dissolution and leaching of drug particles present at the surface prior to formation of the release-controlling gel.

The mechanism of drug release from swell able devices is determined by the relative position of the rubber-glass interface, the rate at which it penetrates the tablet, the diffusion coefficient of the drug and the erosion rate of the gel. When the penetration rate is high as compared to the drug diffusion rate through the swollen gel layer, release is controlled by the diffusion rate of the drug through the gel layer and a diffusion controlled (Fickian) release mechanism is observed. If diffusion of drug through the gel layer is fast as compared to the water penetration rate, release of the incorporated drug is governed by the penetration rate of the interface and zero-order drug release with constant release rate may be achieved. Several dimensionless parameters have been developed to characterize drug release from swelling controlled dosage forms. The Deborah number (De) represents the ratio of the characteristic relaxation time of the swelling polymer ($\tau$) relative to the characteristic diffusion time of the water into the polymer ($\theta$) [6, 7]. The swelling interface number (Sw) represents the ratio of the solvent penetration front velocity ($\nu$) to the rate of drug diffusion through the swollen polymer:

$$De = \theta / \tau Sw = \nu.\delta(t) / ID$$

Where ID is the diffusion coefficient of the drug in the swollen layer and $\delta(t)$ is the thickness of the latter. In order to characterize release behavior, it is necessary to determine both De and Sw since neither of these values is sufficient by itself. Pappas and co-workers have extensively investigated diffusion and solvent

controlled drug release from swell able polymeric devices with various geometries. Release from swell able tablets can easily be analyzed by the following simple equation:

$$M_t / M_\infty = kt^n$$

Where $M_t / M_\infty$ are the fractional drug release, k is a constant representing structural and geometrical characteristic of the device, and n gives the type of release mechanism.

When the rate at which the penetration front moves inward into the glassy core is high as compared to the diffusion rate of dissolved drug molecules through the swollen gel layer, release is controlled by the diffusion rate of the drug through the gel layer and a Fickian diffusion controlled release mechanism with $n \approx 0.5$ is observed. If diffusion of the drug through the gel layer is fast as compared to the solvent penetration rate, release of the incorporated drug is governed by the penetration rate of the interface. For dosage forms with slab geometry, this leads to zero-order release (n=1), which is also called non-Fickian, case II or solvent penetration controlled release. Release profiles with intermediate n-values ($0.5 < n < 1$) are classified as anomalous.[30]

Other swell able polymers, which have been applied in swelling-controlled oral drug delivery systems, which show solvent controlled release, are guar gums, poly (ethylene oxide) (PEO), poly (vinyl alcohol), ethylene-vinyl alcohol copolymers (EVA) and dextran's.

- **Erodible matrix tablets:**

Erodible polymers such as poly anhydrides offer another interesting material platform for zero-order drug release. Like several HPMC grades, upon water penetration, poly anhydrides form a gel-layer, which erodes at a specific rate. By choosing the right polymer composition the thickness of the gel-layer may remain constant with time resulting in a constant release rate until depletion of the drug.

In the last two decades, controlled release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Preparation of drug-

embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for manufacturing controlled release dosage forms because it makes such manufacturing easy. A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers forming insoluble or skeleton matrices constitute the first category of retarding materials, also classed as plastic matrix systems.

The second class represents hydrophobic and water-insoluble materials, which are potentially erodible; while the third group includes polymers those form hydrophilic matrices.

Plastic matrix systems, due to their chemical inertness and drug embedding ability, have been widely used for controlling the release of the drug. Liquid penetration into the matrix is the rate-limiting step in such systems unless channeling agents are used. The hydrophobic and waxy materials, on the other hand, are potentially erodible and control the release of drug through pore diffusion and erosion. Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, does not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier, which controls the drug release from, and the liquid penetration into the center of the matrix system.

The use of hydrophilic polymers is actually the most used method in controlling the release of drugs in the formulation of oral pharmaceutical dosage forms. Hydroxy propyl methylcellulose has been extensively used since the early 1960s as a rate controlling polymer in oral extended-release dosage forms[14].

Hydrophilic matrix systems are popular and versatile controlled release system. Amongst polysaccharide derivatives used to produce such systems, these are a range of cellulose ethers, e.g. hydroxyl propyl methylcellulose (HPMC) and a diverse range of other materials, including sodium alginate, carrageenan, chitosan, and xanthan gum.

### 1.2.3 Materials used as Retardants in matrix tablets

Various polymers have been investigated as drug retarding agents, each presenting a different approach to the matrix system. Based on the features of retarding polymer, matrix systems are usually classified into three main groups. They are:

**Insoluble, Inert**

- Polyethylene
- Polyvinylchloride
- Ethyl cellulose
- Methyl acrylate

**Insoluble, Erodible**

- Carnauba wax
- Stearyl alcohol
- Stearic acid
- Polyethylene glycol
- Castor wax
- Triglycerides

**Hydrophilic**

- Methyl cellulose
- Hydroxy ethyl cellulose
- Hydroxy propyl methyl cellulose
- Carboxy methylcellulose sodium
- Carboxy polyethylene
- Xanthan gum
- Sodium alginate
- Chitosan

## 1.2.5 Methods of preparation: [36]

Three methods may be used to disperse drug and additives in a retardant base.

### 1.2.5.1 Solvent evaporation technique

In this technique a solution or dispersion of a drug and additive is incorporated into molten wax phase and the solvent is removed by evaporation.

#### 1.2.5.2 Compression technique

This involves the compression of granules, which may be prepared by wet granulation or dry granulation technique or direct compression of blend of drug, release retardant material and other additives. Drug, Polymer and the microcrystalline cellulose are passed through suitable sieveno.20. The powders are made into a wet mass by using 1:1 ratio of methanol: water. The wet mass was passed through a suitable sieveno.16 and the granules are dried by keep it in hot-air oven and the dried granules are passed through sieveno.21 and lubricated with talc and magnesium stearate. The lubricated granules were compressed by using rotary tablet punching machine.

#### 1.2.5.3 Fusion technique

Drug and additives are blended into the molten wax matrix at a temperature slightly above melting point more uniform dispersion can be obtained by this technique.

## 1.2.6.2. Process variables:

#### 1.2.6.2.1. Compression force:

For HPMC tablets, although the compression force had a significant effect on tablet hardness, its effect on drug release from HPMC tablets was minimal. It could be assumed that the variation in compression force should be closely related to a change in the porosity of the tablets. However, as the porosity of the hydrated matrix is independent of the initial porosity, the compression force seems to have little influence on drug release.Changes in compression force or crushing strength had minimal effect on drug release from HPMC matrix tablets once critical hardness was reached. Increased dissolution rates were observed when the tablets were found to be extremely soft, and this phenomenon was attributed to a lack of powder compaction, as tablet hardness was only 3 kp.

#### 1.2.6.2.2 Tablet shape:

The size and shape of the tablet for the matrix system undergoing diffusion and erosion might impact the drug dissolution rate. Modification of the surface area for metoprolol tartrate tablets formulated with Methocel® K100LV from the standard concave shape (0.568 sq. in.) to caplet shape (0.747 sq. in.) showed an approximately 20-30% increase in dissolution at each time point.

#### 1.2.6.2.3 Tablet size:

For tablets having the same aspect ratio and drug concentration, tablet size had a very strong influence on the release rate; within 24 hours, 99.8% was released from the small tablets, 83.1% from the medium size and 50.9% from the large tablets. It was hypothesized that the smaller tablets released drug more rapidly due to an increased surface area per volume. Additionally, it was concluded that larger diffusion pathways existed in the larger tablet leading to a decrease in drug release.

### 1.2.6 Mechanism of drug release from matrix tablets:

Figure 5 shows the schematic drug release from matrix diffusion controlled-release drug delivery systems in which the drug homogenously dispersed in hydrophilic matrices, formation of the gel layer and its dynamics as a function of time determines the drug release. Gel layer thickness, which determines the diffusion path length of the drug, corresponds to the distance between the diffusion and erosion fronts. As the swelling process proceeds, the gel layer gradually becomes thicker, resulting in progressively slower drug-release rates; however, due to continuous hydration, polymer disentanglement occurs from the surface of the matrix, resulting in a gradually decreasing depletion zone and an increased dissolution rate.

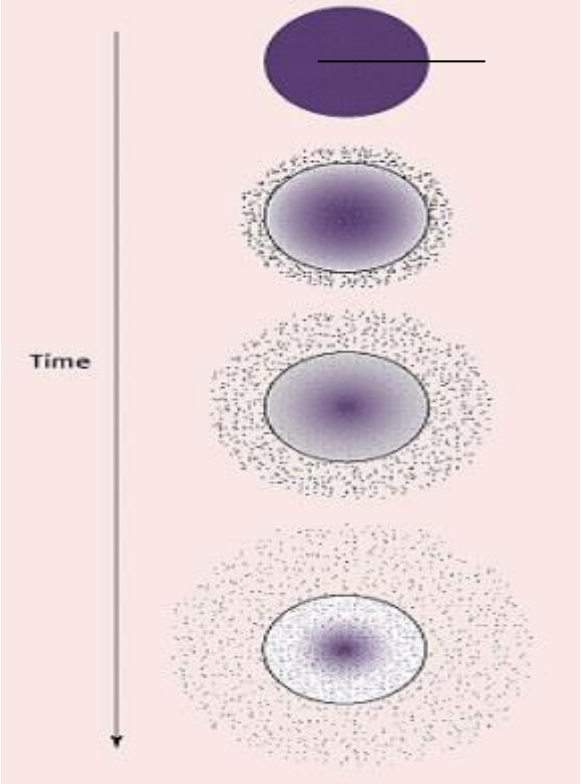


**Fig .5: Drug release from matrix tablets**

## 1.3 KINETICS OF DRUG RELEASE:

The release of drug from controlled devices is via dissolution of the matrix or diffusion of drug through the matrix or a combination of the two mechanisms.

### 1.3.1 Dissolution controlled systems

A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs that are highly water-soluble. This can be done by:

- preparing an appropriate salt or derivative
- coating the drug with a slowly dissolving material – encapsulation dissolution control
- incorporating the drug into a tablet with a slowly dissolving carrier – matrix dissolution control (a major disadvantage is that the drug release rate continuously decreases with time)

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. The dissolution process at steady-state is described by the Noyes-Whitney equation:

$$dc/dt = Kd.A.(Cs-C) = D/h.A.(Cs-C) \quad \text{Eq:1.}$$

Where:-

dc/dt - dissolution rate

kd - the dissolution rate constant (equivalent to the diffusion coefficient divided by the thickness of the diffusion layer D/h)

D - Diffusion coefficient

Cs - saturation solubility of the solid

C - Concentration of solute in the bulk solution

Equation 1,Predicts that the rate of release can be constant only if the following parameters are held constant: surfacearea, diffusion coefficient, and diffusion layer thickness and concentration difference.

However, under normal conditions, it is unlikely that these parameters will remain constant, especially surface area, and this is the case for combination diffusion and dissolution systems.

## 1.3.2 Diffusion controlled systems:

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier, which is usually a water-insoluble polymer.

In general, two types or subclasses of diffusion systems are recognized: reservoir devices and matrix devices[41]

## 1.3.2.1. Reservoir devices:

ER formulations, where film coating constitutes the main factor in controlling drug release. Examples of materials used to control drug release include hardened gelatin, methyl or ethyl cellulose, polyhydroxymethacrylate, methacrylate

ester copolymers, and various waxes. Ethyl cellulose and methacrylate ester copolymers are the most commonly used systems in the pharmaceutical industry.

### 1.3.2.2. Matrix extended release systems

In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix [41].

Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release;

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;

c) The diffusion coefficient of drug in the matrix remains constant (no change occurs in the characteristics of the polymer matrix[41] .

d) The bathing solution provides sink conditions at all times;

e) No interaction occurs between the drug and the matrix;

f) The total amount of drug present per unit volume in the matrix is substantially greater than the saturation solubility of the drug per unit volume in the matrix (excess solute is present)

g) Only the diffusion process occurs [44] .

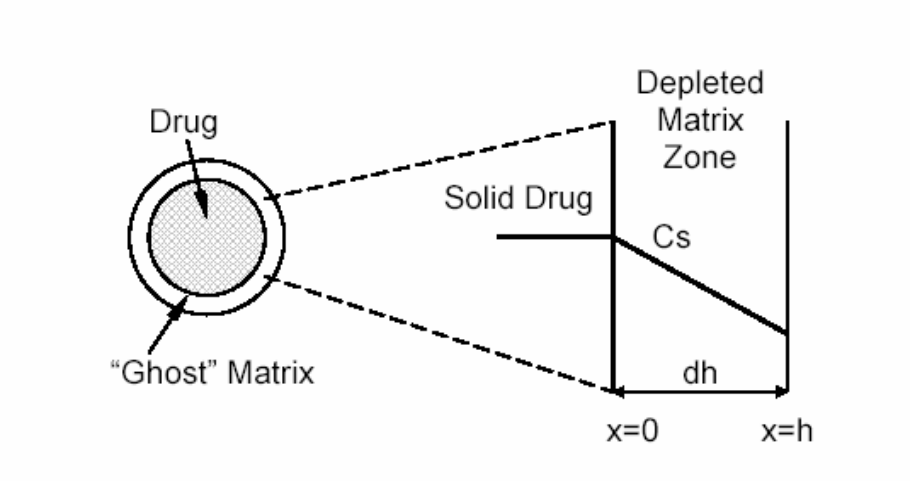


**Fig. 6 : Schematic representation of a matrix release system**

Release from a monolithic matrix system can be graphically depicted as in shown in Figure 1

The release behaviour for the system can be mathematically described by the following equation:

$$\frac{dM}{dh} = Co.dh - \frac{Cs}{2}$$

Eq :2

Where,

dM - change in the amount of drug released per unit area

dh - change in the thickness of the zone of matrix that has been depleted of drug

Co - total amount of drug in a unit volume of matrix

Cs - saturated concentration of the drug within the matrix.

Additionally, according to diffusion theory:

$$dM = Dm.\frac{Cs}{h}.dt$$

Eq: 3

Where,

Dm - is the diffusion coefficient in the matrix.

h - Thickness of the drug-depleted matrix

dt - change in time

By combining equation 2 and equation 3 and integrating:

$$M = [Cs.Dm.(2Co-Cs).t]^{1/2}$$

Eq :4

When the amount of drug is in excess of the saturation concentration, then:

$$M = [2.Cs.Dm.Co.t]^{1/2}$$

Eq **:5**

Equation 4 and equation 5 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line.

Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

$$M = [Ds.Ca.p/T.(2Co-p.Ca).t]^{1/2}$$

Eq **:6**

Where:

p - Porosity of the matrix

t - Tortuosity

Ca - solubility of the drug in the release medium

Ds - Diffusion coefficient in the release medium.

T – Diffusional pathlength

For pseudo steady state, the equation can be written as:

$$M = [2D.Ca.Co.p/T.t]^{1/2}$$

Eq **:7**

The total porosity of the matrix can be calculated with the following equation:

$$P=Pa+Co/\rho+Cex/\rho ex$$

Eq:8

Where:

P – Porosity

ρ – Drug density

Pa – porosity due to air pockets in the matrix

ρex – density of the water soluble excipients

Cex – concentration of water soluble excipients

For the purpose of data treatment, equation 6 can be reduced to:

$$M = k.t\ 1/2$$

Eq :9

Where, k is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled.

If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity

- Polymer system forming the matrix
- Solubility of the drug .

# REVIEW OF LITERATURE

## 2.1 EXTENDED RELEASE MATRIX SYSTEMS:

**Mohammad MahiuddinTalukdar et.al** [38] conducted a study on xanthan gum and hydroxylpropylmethylcellulose as matrices for controlled release drug delivery1. Composition and in vitro drug release behaviour. In respect of controlled drug release behaviour xanthan gum matrices have some important pharmaceutical as well as economic advantages (e.g., absence of initial burst release, higher drug-retarding ability, and more reproducibility in drug release, and the possibility of zero-order release kinetics) over HPMC matrices. Considering the influence of ionic strength of the medium on drug release behaviour xanthan gum has a disadvantage that the drug release is influenced by the total salt concentration within the range of gastro-intestinal tract, while the drug release from HPMC matrices is independent of ionic strength. But this ionic strength dependency should not be considered as a total failure of XG for controlling the drug release. Compaction characteristics between the two polymers are quite similar, but the flow ability of xanthan gum is better than that of HPMC.

**Johan Hjartstamet.al**[39] studied the effect of hydroxyl group content in ethyl cellulose on permeability in free films and coated membranes the change in the water permeability, glass transition temperature, and mechanics properties of ethyl cellulose with different degrees of substitution are presented. Studies of the hydroxyl group content on the polymer chain indicate that the mechanical properties of a free film decrease as the hydroxyl group content decreases. This is thought to be due to the lower solubility of ethyl cellulose with a lower degree of substitution, as determined by the interaction constant in ethanol and the ability of the film with a high hydroxyl group content to hold more water. Furthermore, an increase in hydroxyl group content, the higher the drug release rate and, at the same time, the decrease in Vickers hardness.

**Wikstrand John et.al**[40] conducted a study about pharmacokinetic considerations of formulation, extended release metoprolol Succinate in the treatment of Heart failure. Extended release metoprolol succinate is a controlled release formulation designed to deliver metoprolol succinate at a near constant rate

for approximately 20hr, independent of food intake and gastrointestinal pH. Once daily dosing of ER metoprolol succinate 12.5-200mg produces even plasma concentrations over a 24h period, without the marketed peaks and troughs characteristically observed with the immediately release formulation. This leads to consistent beta -1-blockade over 24h, while maintaining cardio selectivity at a dose upto 200Mg daily, Pharmacokinetics studies have also been performed in heart failure patients and have demonstrated that ER metoprolol succinate is associated with a more pronounced and even beta-1-blockade over a 24h period than IR formulation, The efficiency and good tolerability of ER metoprolol succinate in heart failure patients has now been demonstrated in a large-scale trial.

**Mamoru Fukuda et al**[41] studied the properties of sustained release hot-melt extrudedtablets containing chitosan and xanthan gum. The aim of this study was to investigate the influence of pH, buffer species and ionic strength on the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets containing chitosan and xanthan gum prepared by a hot-melt extrusion process. Drug release from hot-melt extruded (HME) tablets containing either chitosan or xanthan gum was pH and buffer species dependent and the release mechanisms were controlled by the solubility and ionic properties of the polymers. All directly compressed (DC) tablets prepared in this study also exhibited pH and buffer species dependent release. In contrast, the HME tablets containing both chitosan and xanthan gum exhibited pH and buffer species independent sustained release. When placed in 0.1N HCl, the HME tablets formed a hydrogel that functioned to retard drug release in subsequent pH 6.8 and 7.4 phosphate buffers even when media contained high ionic strength, whereas tablets without chitosan did not form a hydrogel to retard drug release in 0.1N HCl. The HME tablets containing both chitosan and xanthan gum showed no significantchange in drug release rate when stored at 40 ◦C for 1 month, 40 ◦C and 75% relative humidity (40 ◦C/75% RH) for 1 month, and 60 ◦C for 15 days.

**VinessPillay and Reza Fassihi et.al**[42]developed a novel monolithic drug delivery system for highly water-soluble bioactive agents to follow pH-independent zero-order kinetics is described. The system utilizes a hydrophilic gel-based swellable polymeric material (polyethylene oxide), a model drug (metoprolol

tartrate, 100% water soluble at 25°C) and different electrolytes, such as sodium carbonate and/or pentasodiumtripolyphosphate. Based on the induction of in situ intra-gel chemical reactions between different ionic species, drug and polymer, a heterogeneous structure manifested as 'peripheral boundary stiffening,' is accomplished. The consequence of these interactions essentially include the development of gradient-controlled matrix swelling as elucidated through textural profiling, which may contribute to inhibition of drug solubility and its outward diffusion. Analysis of textural profiles and photo microscopy distinctly provides information on the disposition of peripheral boundary densification for the electrolyte-containing matrices. Electrolytic conductivity measurements performed with the simultaneous analysis of matrix swelling showed that sodium carbonate forms a highly reactive matrix within the first 3 h of medium penetration. On the other hand, larger molecules such as pentasodiumtripolyphosphate maintain a constant conductivity level, which may be related to its lower solubility and diffusion in comparison to sodium carbonate. Based on model fitting and statistical analysis, it is shown that drug release kinetics were adequately described by $M_t/M_\infty=k_0t$, with zero-order release rate constant $k_0$ of 0.054 $h^{-1}$. This novel approach in formulation development could potentially be used for constant rate delivery of highly soluble bioactive agents over an extended period for specific biopharmaceutical needs.

**Thomas Durig et al** [43] studied the effect of guar-based monolithic matrix systems: effect of ionizable and non-ionizable substances and excipients on gel dynamics and the release kinetics Tablet dissolution, erosion and water uptake studies were carried out using a modified USP 23 Apparatus 2 method. The kinetics of gel strength and texture development were studied by textural analysis. Near linear drug release over 24 h was obtained from formulations containing water soluble, ionizable sodium chloride and glycine. The contribution of Fickian release to overall drug release was lowest for these formulations and was correlated with greater gel strength and lower water uptake in the early time period. For soluble sugars (lactose and sucrose) the Fickian contribution to overall drug release was large and associated with pronounced curvilinear profiles. Water uptake was greatest

for these additives (450% in 6 h). The lowest water uptake and negligible matrix erosion was observed for microcrystalline cellulose. Release from this formulation was predominantly Fickian. It was found that the physicochemical nature of added excipients significantly influences the release kinetics from guar-based formulations. Ionic, water soluble materials (sodium chloride, glycine) reduce initial hydration of the matrix and thus have the ability to limit the initial rapid diffusion of drug and to sustain near linear release over 24 h.

**Howard et.al**[44]studied the controlled release formulation is provided which release a pharmaceutical of a basic character at a controlled rate regardless of the pH of the environment, Which formulation includes a basic pharmaceutical upto about 45% by weight of a pH dependent polymer which is a salt of alginic acid, such as sodium alginate, upto about 35% weight of a pH independent hydrocarbon gelling agent having a viscosity of upto about 100,000 centiposes in 2% solution at $20^{0}$ C., binder and excipient's.

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**Salsa et.al**[45] reported the oral controlled- release dosage forms.1. Cellulose ether polymers in hydrophilic matrices. An appropriate designed controlled-release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controller the rate of drug delivery to the target tissue.Hydrophillic matrices are an interesting option when developing an oral controlled-release formulation. The present study focuses on oral controlled-release dosage forms and the application of cellulose ether polymers in hydrophilic matrices.

**Appelgren et.al**[47]studied the pharmaceutical composition comprising of metoprolol succinate. The present invention related to metoprolol succinate, a new therapeutically active compound and pharmaceutical preparations comprising this new compound.

# AIM, OBJECTIVE

# &

# PLAN OF WORK

# 3.AIM

The aim of the present study relates to the development of extended release matrix tablets containing metoprolol succinate for the treatment of antihypertensive.

# 4.OBJECTIVES AND PLAN OF WORK

Controlled release drug delivery systems are designed by different techniques like enteric coating, osmotic pump, pro drugs, transdermal patches and matrix tablets. Among the various techniques used, recently the attention of pharmaceutical researchers has been attracted by the matrix tablets because of their ease of manufacturing. Different types of polymers are used to control the release of drugs from the dosage forms for absorption by the human body. Though a variety of polymeric substances are available to serve as release retarding matrix materials there is a continued need to develop new, safe and effective release retarding materials for matrix tablets. Natural gums and polysaccharides and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms due to their non-toxicity, low cost and free availability. Natural gums and hydrophilic polymers and where in contact with water, they are hydrated to form a gel. Because of this property natural gums like gum karaya, xanthan gum and olibanun gum have been reported as good matrix materials for sustained release dosage forms.

Xanthan gum is compatible with variety of active ingredients and other excipients and readily hydrates, absorb water and swell quickly. Because of their hydrophilic nature and highly cross-linked structure they are more suitable material for use in controlled release drug delivery systems.

Metoprolol succinate is an Antihypertensive drug under β1 adrenergic receptor antagonist. Being a class 1 molecule under BCS classification it eliminates faster from the body (conventional dosage form).It's short biological half life (3-7hrs) that calls for frequently daily dosing (2 to3 times) and therapeutic use in chronic anti-hypertensive disease necessitates its formulation into extended release dosage form. So it is formulated as extended release matrix formulation.

The objective of the present study was to formulate metoprolol succinate extended release matrix tablets using xanthan gum (natural polymer) and to elucidate the release kinetics of metoprolol succinate from xanthan gum-matrices. Here, an attempt was made to develop extended release metoprolol succinate matrix tablets

## Hence, the objectives of the present work include:

- To prepare a stable and robust formulation containing metoprolol succinate and to compare with the innovator product Toprol XL.
- To prepare a pharmaceutical equivalent formulation of metoprolol succinate matrix formulation.
- To prepare a stable and robust formulation of metoprolol succinate matrix tablet meeting USP specifications.
- To prepare a stable and robust formulation of extended release matrix formulation for BCS class1 molecule, metoprolol succinate.

## 4.1Plan of work:

**PREFORMULATION STUDIES**

- Physical parameters: Bulk density
  Tapped density
  Compressibility index
  Angle of repose
  Hausner's ratio
- Drug –excipient compatibility studies

- **ESTIMATION OF DRUG**
- **FORMULATION DEVELOPMENT**
- **EVALUATION OF FORMULATION**

- Physical parameters**:** Hardness,
  Friability,
  Weight variation
  Drug content
  Dissolution

- **Stability Studies**

# DRUG AND EXCIPIENT PROFILE

## 5.1.DRUG PROFILE:

- **Physico-chemical properties:**

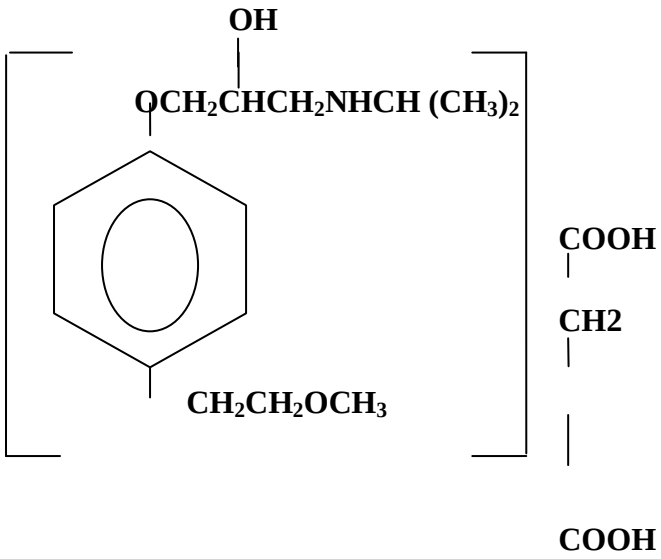
**Drug** : Metoprolol succinate

**Description :** white powder, free from the visible extraneous matter.

**Chemical Name** : 2-propanol, 1-(4-(2-methoxyethyl)phenoxy) -3-((1-methylethyl) amino)-, (±) butaedioate(2:1)(salt)

**Molecular Formula :** $(C_{15}H_{25}NO_3)_2C_4H_6O_4$

**Structure:**




**Molecular weight** **:** 652.81

**Melting point** **:** 120°c

**Solubility** **:** Freely Soluble in water, Soluble in methanol,

Sparingly soluble in alcohol &

Practically insoluble in dichloromethane

**BCS Class** **:** Class 1

- **PharmacoKinetics/Dynamics:**

**Tmax** **:1.5-2 hrs oral regular; 6-12 hrs (longacting)**

**Bioavailability** **:50%**

**Plasma protein binding** **:12%**

**Route of metabolism** **:Hepatic by oxidative deamination**

**Route of excretion** **:Renal**

**Halflife** **:3-7hrs**

**$P^{ka}$** **:9.68**

- **Mechanism of action:**

Metoprolol is a β1 selective adrenergic receptor blocking agent. The precise mechanism of anti-hypertensive effect is not known. Possible mechanisms include reduced cardiac output, decreased sympathetic out flow to peripheral vasculature, and inhibition of renin release by the kidneys.

- **Therapeutic Uses:** Antianginal and Antihypertensive

- **Dosage:**

Tablet, Extended release, as Succinate: 25mg, 50mg, 100mg, 200mg [expressed as mg equivalent to tartarate]

- **Over Dose:**

  Cardiac disturbances, CNS toxicity, Bronchospasm, Hypoglycemia, and Hyperkalemia

- **Storage:**

  Tablet:Store between $15^0$C to $30^0$C

## 5.2. EXCEPIENTS PROFILE:

### 5.2.1.Xanthan gum

**General Description:**

**i. Name** **: Nonproprietary**BP: Xanthan gum, USPNF: Xanthangum

**ii. Synonyms** **:** Corn Sugar Gum; E415; Keltrol; polysaccharide B-1459; Rhodigel; Vanzan NF; Xantural.

**iii. Chemical Name** **:** Xanthan gum

**iv. Empirical Formula** **:** $(C_{35}H_{49}O_{29})_n$

**v. Molecular Weight** **:** Approximately $2 \times 10^6$

**vi. Functional Category** **:** Stabilizing agent, suspending agent, viscosity-increasing agent.

**Description:**

Xanthan gum occurs as a cream or white colored, odorless, free-flowing, fine powder.

**Properties**

**Acidity/alkalinity** **:** pH = 6.0–8.0 for a 1% w/v aqueous Solution.

**Freezing point** **:** 0°C for a 1% w/v aqueous solution.

**Heat of combustion** **:** 14.6 J/g (3.5 cal/g)

**Melting point** **:** 270°C.

**Particle size distribution** **:** Various grades with different particle sizes are available; for example, 100% less than 180 μm in size for Keltrol CG; 100% less than 75 μm in size for Keltrol CGF; 100% less than 250 μm, 95% less than 177 μm in size for Rhodigel; 100% less than 177 μm, 92% less than 74 μm in size for Rhodigel 200.

**Refractive index** **:** $n^{20}_{D}$ = 1.333 for a 1% w/v aqueous solution.

**Solubility** **:** PracticallSy insoluble in ethanol and ether; Soluble in cold or warm water.

**Specific gravity** **:** 1.600 at 25°C

**Viscosity (dynamic)** **:** 1200–1600 mPa s (1200–1600 cP) for a 1% w/v Aqueous solution at 25°C.

**Stability**

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at (pH 4–10) and temperatures of 10–60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for

example, viscosity is reduced. Solutions are also stable in the presence of enzymes, salts, acids, and bases.

**Storage Conditions**

The bulk material should be stored in a well-closed container in a cool, dry place.

**Incompatibilities**

Xanthan gum is incompatible with oxidizing agents, some tablet film-coatings, carboxymethylcellulose sodium, dried aluminum hydroxide gel and some active ingredients such as amitriptyline, tamoxifen and verapamil.

**Safety**

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and food products and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient.The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body-weight.

**Related Substances**

Ceratonia; guar gum

**Applications in Pharmaceutical Formulation or Technology**

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over a wide pH and temperature range. Xanthan gum gels show pseudo plastic behavior, the shear thinning being directly proportional to the shear rate. The viscosity returns to normal immediately on release of shear stress

Although primarily used as a suspending agent, xanthan gum has also been used to prepare sustained-release matrix tablets. Xanthan gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin, thereby helping in the prolonged retention of the dosage form in the pre-corneal area

Recent studies have revealed that xanthan gum can also be used as an excipient for spray-drying and freeze-drying processes for better results.

Xanthan gum can be used to increase the bio adhesive strength in vaginal formulations and as a binder in colon specific drug delivery systems. Xanthan gum is also used as a hydrocolloid in the food industry and in cosmetics it has been used as a thickening agent in shampoo.

## 5.2.2. Microcrystalline Cellulose

**Physico chemical properties**

**Description**

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle size Stretching and moisture grades that have different properties and applications.

**Formula** **:** ($C_6H_{10}O_5$)

**Molecular weight** **:** n~220

**Density (bulk)** **:** 0.32 $g/cm^3$

**Density (tapped)** **:** 0.45$g/cm^3$

**Density (true)** **:** 1.512-1.668 $g/cm^3$

**Melting point** **:** Chars at 260-270 $^0$ C.

**Solubility** **:** Slightly soluble in 5% W/V sodium hydroxide solution;

Practically insoluble in water, dilute acids, and most organic solvents.

**Application in pharmaceutical Formulation Technology**

Microcrystalline cellulose is widely used in pharmaceuticals primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct-compression process. In addition to its use as a binder /diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

**Functional Category**

Adsorbent; suspending agent, tablet and capsule diluent, tablet disintegrant.

**Use of Microcrystalline cellulose**

| Use | Concentration (%) |
|---|---|
| Adsorbent | 20-90 |
| Anti-adherent | 5-20 |
| Capsule binder/ diluent | 20-90 |
| Tablet disintegrant | 5-15 |
| Tablet binder/ diluent | 20-90 |

**Incompatibilities**

Microcrystalline cellulose is compatible with strong oxidizing agents

**Method of Manufacture**

Microcrystalline cellulose is manufactured by the controlled hydrolysis with dilute mineral acid solutions of a-cellulose obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad-size distribution

**Safety**

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a nontoxic and non-irritant material. Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may, however, have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations

## 5.2.3.Hydroxypropylmethylcellulose (HPMC)

**Nonproprietary names:**

BP**:**HypromelloseJP: Hydroxypropylmethylcellulose,PhEur: Hypromellosum,USP: Hypromellose.

**Synonyms:**

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.

**Chemical name:** Cellulose hydroxypropyl methyl ether.

**Functional category:**

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

**Description:**

Hypromellose is an odourless and tasteless, white or creamy-white fibrous or granular powder.

**Solubility:**

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

**Viscosity:**

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions.

**Stability and storage conditions:**

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material. Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage. However, aqueous solutions are liable to microbial spoilage and should be preserved with an

antimicrobial preservative, when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions; benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be re-dispersed on cooling by shaking.

Hypromellose powder should be stored in a well-closed container, in a cool and dry place.

**Applications:**

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder, in film-coating and as a matrix for use in extended-release tablet formulations.Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Sizes and moisture grades that have different properties and applications.

## 5.2.4.Magnesium Stearate

**Description:**

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

**Molecular weight :** 591.34

**Structural Formula :** $[CH3 (CH_2)_{16} COO]_2 Mg$

**Crystalline Forms:**

High purity magnesium stearate has been isolated as a trihydrate, adihydrate and an anhydrate

**Flow ability :** Poorly flowing, cohesive powder

**Meltingrange :** 117-150$^{o}$C (commercial samples) 126-130$^{o}$C (high purity magnesiumstearate)

**Solubility:**

Practically insoluble in ethanol, ethanol (95 %), ether and water; slightly soluble in warm benzene and warm ethanol (95 %)

**Specific surface area :** 1.6-14.8 $m^2/g$

**Functional category :** Tablet and capsule lubricant

**Applications in Pharmaceutical Formulation Technology:**

It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 % and 5.0 % w/w.

**Incompatibilities:**

Incompatible with strong acids, alkalis and iron salts.Strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins and most alkaloid salts

**Method of Manufacture:**

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide or carbonate with stearic acid at elevated temperatures.

**Safety:**

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation.

# METHODOLOGY

## 6.1. MATERIALS:

**Table 2. List of materials used**

| S.NO | MATERIAL | SOURCE |
|---|---|---|
| 1. | Metoprolol succinate | Dr.Reddylabs |
| 2. | Xanthan gum | M/S Jungbuzlauer, Austria |
| .3. | MCC | FMC |
| 4. | HPMC5cps | Colorcon |
| 5. | HPMC100cps | Colorcon |
| 6. | Magnesium stearate | Ferro |
| 7. | Lactose | DMV |
| 8. | Potassium di hydrogen phosphate | Merck |
| 9. | Sodium hydroxide | Merck |
| 10. | Potassium di hydrogen phosphate monohydrate | Merck |
| 11. | Ortho phosphoric acid | Qualigens |
| 12. | Acetonitrile | S.D fine chemicals |
| 13. | Ethanol | Hong yang |
| 14. | HCL | Merck |

| S.NO | EQUIPMENTS | SOURCE |
|---|---|---|
| 1. | Digital balance | Sagtoriouse |
| 2. | Electronic balance | Metler |
| 3. | UV-Visible spectrophotometer | Perkinelmar-Win lab |
| 4. | Rapid dryer | Retsct TG 200 |
| 5. | Tapped density apparatus (USP) | Electro Lab |
| 6. | Planetary mixer | Kenwood |
| 7. | RMG | Sacal |
| 8. | FBC | Glatt |
| 9. | Bleder | Vamp |
| 10. | Multi mill | Ganson |
| 11. | Shifter | Gansons limited |
| 12. | Rotary compression machine | Cadmach, 16 Stations |
| 13. | Fribilator | Electro Lab |
| 14. | Hardness tester | Thermo lab |
| 15. | Dissolution apparatus | Lab India, India |
| 16. | Digital pH meter | Thermo andMetrom |
| 17. | Vernier calipers | |
| 18. | HPLC | Agilent-Empower and waters-Breeze |
| 19. | Glass Ware | Qualigens |
| 20 | Sieve shaker | Retsch |

| | | |
|---|---|---|
| **21** | **FTIR** | **Thermo electronic corporation** |

**TABLE 3.: List Of Equipments**

| | | |
|---|---|---|
| **22** | **Sonicator** | **Bandelinsonorex** |
| **23.** | **Centrifuge** | **Her mle** |
| **24.** | **Sieve Shaker** | **Lab companion** |
| **25** | **Vaccum oven** | **Mack** |
| **26** | **Water bath** | **Thera ml** |
| **27** | **KF titrator** | **Metromin** |
| **28** | **Stirrer** | **Remi motors** |
| **29** | **LOD Machine** | **Mettler Toledo** |

## 6.2.PREFORMULATION STUDIES:

### 6.21.Drug – Excipient compatibility studies:

The excipients weighed according to mentioned ratio and sifted through BSS # 36 and blended together. The mixture placed in two vials. One set of vials are stored at $4^0$C as control. The set was stored at $40^0$C/75% RH. The caps of the vials which were kept at $40^0$C/75% RH were punctured for the permeation of moisture. The vials observed after every week and compared with vials kept at $4^0$C as control for any physical incompatibility like lump formation, colour change. Results are shown in below table.

### 6.2.2.Flow Properties determination:

Certain methods are used to measure granulation and powder characteristics in order to monitor granulation suitability for tableting. Good flow properties are essential for the transport of the material through the hopper into and through the feed frame and in to dies.

**Angle of repose**

The frictional force in a loose powder can be measured by the angle of repose θ. It is defined as, the maximum angle possible between the surface of the pile of the granules and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. The angle of repose was determined by the funnel method suggested by Newman. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated using the following formula

$$\tan \theta = h/r$$

Therefore $$\theta = \tan^{-1} ( h/r )$$

Where,

θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

**Table 3: Flow Properties and Corresponding Angle of Repose**

| Flow Property | Angle of Repose (Degrees) |
|---|---|
| Excellent | 25 – 30 |
| Good | 31 -35 |
| Fair (aid not needed) | 36 – 40 |
| Passable (may hang up) | 41 – 45 |
| Poor (must agitate, Vibrate) | 46 – 55 |
| Very poor | 56 – 65 |

| | |
|---|---|
| Very, Very poor | > 66 |

**Bulk Density**

Density is defined as weight per unit volume. Bulk density $P_b$ is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm$^3$. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. There are two types of bulk density.

The particles are pack in such a way so as to leave large gaps between their surfaces resulting up in light powder of low bulk density. Here the smaller particles shift between the large particles resulting in heavy powder of high bulk density. Bulk density is very important in the size of containers needed for handling, shipping and storage of raw material and blend. It is also important in size blending equipment

Apparent bulk density ($P_b$) was determined by pouring blend into a graduated cylinder. The bulk volume ($V_b$) and weight of the powder (M) was determined. The bulk density was calculated by using the following formula

$$\mathbf{P_b = M/ V_b}$$

Where,

$P_b$ = Bulk Density

M = Weight of sample in gm

$V_b$ = Final volume of blend in cm$^3$

**Tapped Density**

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. The tapped density was calculated by using the following formula

Where, $\mathbf{P_t} = \mathbf{M / V_t}$

$\mathbf{P_t}$ = Tapped Density

M = Weight of the sample in gm

$\mathbf{V_t}$ = Tapped volume of blend in $cm^3$

**Compressibility Index and Hausner's ratio**

In recent years, the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the Hausner's ratio are determined by measuring both the bulk volume and tapped volume of a powder.

**Basic methods for the determination of compressibility Index and Hausner's Ratio**

While there are some variations in the method of determining the compressibility index and Hausner's ratio, the basic procedure is to measure the unsettled apparent volume ($V_0$), and the final tapped volume ($V_f$), of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner'sratio are calculated as follows

$$Compressibility\ Index = 100 \times \frac{V_0 - V_f}{V_0}$$

$$Hausner\ Ratio = \frac{V_0}{V_f}$$

Alternatively, the compressibility index and Hausner ratio may be calculated using measured values of bulk density and tapped density as follows

Compressibility Index = 100 × Tapped density / Bulk density

Hausner Ratio = Tapped density/ Bulk density

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping. For the compressibility index and the Hausner's ratio, the generally accepted scale of flow ability is described by Carr. The values are tabulated in the below table – 4.

### 6.3API Characterization

**Determination of Bulk Density, tapped density:**

A known amount of metoprolol succinate was taken in 50 ml measuring cylinder which was placed in Electro lab Tapped Density Apparatus(method USP-I). Initial volume ($V_0$) of the cylinder was noted and then the cylinder was tapped 500 times and volume was measured. Then further an additional 750 tappings were repeated. No difference was noted between the volumes between two tappings (500 and 750). The final volume (V) was considered after completion of 750 taps. The values obtained are reported in the table: 3

### 6.4. FORMULATION AND EVALUUATION OF MATRIX FORMULATIONS

**FORMULATIONS:**

**6.4.1.Method of Selection** : Extended release tablets of metoprolol succinate were formulated using three methods they were

- DIRECT COMPRESSION
- DRY GRANULATION
- WET GRANULATION

**Formulation X1A**

**DIRECT COMPRESSION:**

Table 4 gives details of ingredients used in composition preparation of metoprolol succinate tablets by direct compression for X-1A.

Composition of the formulation X1A

Table :4

| **INGREDIENTS** | **X-1A** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 24.3 |
| MCC(AVICEL) | 229.2 |
| HPMC5cps | 15.5 |
| Magnesium stearate | 2.4 |
| Total | 297 |

**Procedure**

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, binder, diluents, lubricant through BSS # 40 sieve separately
3. Blended metoprolol succinate, polymer, binder, diluents in a poly-bag
4. Step 3 materials were blended with sifted lubricant
5. Compressed the blend of Step 4 materials into round concave shaped tablets with the help of 8mm concave shaped punches

**Formulation X1B**

DRY GRANULATION:

Table 5 gives details of ingredients used in composition preparation of metoprolol succinate tablets by dry granulation for X-1B.

Composition of the formulation X1B

Table : 5

| **INGREDIENTS** | **X-1B** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.5 |
| Xanthan gum | 28.8 |
| MCC (AVICEL 102) | 228 |
| HPMC5cps | 13.2 |
| Magnesium stearate | 2.4 |
| Total | 297.9 |

**Procedure:**

Weighed all ingredients accurately

1. Sifted metoprolol succinate, polymer, binder, diluents, lubricant through BSS # 40 sieve separately
2. Blended metoprolol succinate, polymer, binder, diluents in a poly-bag
3. Step 3 materials were blended with sifted lubricant
4. That step 4 material passed through roll compact machine
5. That step 5 material passed through #25 mesh
6. Compressed the blend of Step 6 materials into round concave shaped tablets with the help of 8mm concave shaped punches

**Formulation X1C**

**WET GRANULATION**:

Table 6 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation by X 1C.

Composition of the formulation X1C

Table :6

| **INGREDIENTS** | **X-1C** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.7 |
| Xanthan gum | 30.2 |
| MCC (AVICEL 102) | 224.6 |
| HPMC5cps | 14.3 |
| Water | q.s |
| Magnesium stearate | 2.4 |
| Total | 297.2 |

Procedure:

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in planetary mixer
4. Prepared HPMC 5cps binder solution (Take 95 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$C for 45 minutes. (Up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve

9. Sifted extra granular lubricant through BSS # 40 and blended with material of Step8
10. Compressed the blend of Step 9 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X2**

**WET GRANULATION**:

Table 7 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation by X -2.

Composition of the formulation X2

Table :7

| **INGREDIENTS** | **X-2** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 68.4 |
| MCC (AVICEL 102) | 186.3 |
| HPMC5cps | 13.2 |
| Water | q.s |
| Magnesium stearate | 2.4 |
| Total | 295.9 |

**Procedure:**

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in planetary mixer
4. Prepared HPMC 5cps binder solution (Take 95 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min

6. Wet granules are formed
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular lubricant through BSS # 40 and blended with material of Step8
10. Compressed the blend of Step 9 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X3**

**WET GRANULATION**:

Table 8 gives details of ingredients used in composition preparation of metoprolol succinate tablets by direct compression for X -3

Composition of the formulation X3

Table : 8

| **INGREDIENTS** | **X-3** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 122.4 |
| MCC (AVICEL 102) | 132.2 |
| HPMC5cps | 14.1 |
| Water | q.s |
| Mg.stearate | 2.4 |
| Total | 296.7 |

Procedure:

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve

3. That step 2 material is dry mixed for 20 min in planetary mixer
4. Prepared HPMC 5cps binder solution (Take 95 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition of above solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular lubricant through BSS # 40 and blended with material of Step8
10. Compressed the blend of Step 9 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X4**

**WET GRANULATION**:

Table 9 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation for X -4

Composition of theformulation X4

Table :9

| **INGREDIENTS** | **X-4** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 221.6 |
| MCC (AVICEL 102) | 35.7 |
| HPMC5cps | 13.8 |
| Water | q.s |
| Mg.stearate | 2.4 |
| Total | 299.9 |

**Procedure:**

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in planetary mixer
4. Prepared HPMC 5cps binder solution (Take 95 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition of above solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular lubricant through BSS # 40 and blended with material of Step8
10. Compressed the blend of Step 9 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X5**

**WET GRANULATION**:

Table 10 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation for X -5

Composition of the formulation X5

Table : 10

| **INGREDIENTS** | **X-5** |
|---|---|
| | **mg/tab** |
| **Metoprolol succinate** | 25.6 |
| **Xanthan gum** | 221.6 |
| **MCC (AVICEL 102)** | 35.7 |
| **HPMC 5cps** | 13.8 |
| **Water** | q.s |
| **Mg.stearate** | 2.4 |
| **Total** | 299 |

**Procedure:**

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in 5Lt RMG(5000Tabs)
4. Prepared HPMC 5cps binder solution (Take 150 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition of above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (Up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular lubricant through BSS # 40 and blended with material of Step8
10. Compressed the blend of Step 9 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X6**

**WET GRANULATION**:

Table 11 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation for X-6

Composition of the formulation X6

Table : 11

| INGREDIENTS | X-6 |
|---|---|
| | mg/tab |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 229.2 |
| MCC (AVICEL 102) | 24.3 |
| HPMC5cps | 15.5 |
| Water | q.s |
| Mg.stearate | 2.4 |
| Total | 297 |

Procedure:

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in 3Lt RMG(for 2000 tabs)
4. Prepared HPMC 5cps binder solution (Take 150 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition of above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular lubricant through BSS # 40 and blended with material of Step8
10. Compressed the blend of Step 9 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X7**

**WET GRANULATION :**

Table 12 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation for X-7

Composition of the formulation X7

Table : 12

| **INGREDIENTS** | **X-7** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 122.2 |
| MCC (AVICEL 102) | 132.1 |
| HPMC5cps | 14.1 |
| Water | q.s |
| Mg.stearate | 2.4 |
| Total | 296.4 |

Procedure:

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in 3Lt RMG(for 2000tabs)
4. Prepared HPMC 5cps binder solution (Take 180 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition of above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular lubricant through BSS # 40 and blended with material of Step8
10. Compressed the blend of Step 9 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X5 EGI**

**WET GRANULATION :**

Table13 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation for X-5 EG – 1

Composition of the formulation X5 EG1

Table :13

| **INGREDIENTS** | **X-5 EG-1** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 200.4 |
| MCC (AVICEL 102) | 35.9 |
| HPMC5cps | 13.8 |
| Water | q.s |
| HPMC K100M | 21.1 |
| Mg.stearate | 2.4 |
| Total | 299.5 |

Procedure:

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in 3Lt RMG(for 2000tabs)
4. Prepared HPMC 5cps binder solution (Take 150 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular retardant through BSS # 40 and blended with material of step 8
10. Sifted extra granular lubricant through BSS # 40 and blended with material of step 9

11. Compressed the blend of step 10 in to round concave shaped tablets with the help of 8 mm concave shaped punches.

**Formulation X5 EG2**

**WET GRANULATION**:

Table14givesdetailsofingredientsusedincompositionpreparationofmetoprololsuccinatetabletswet granulation for X -5 EG-**2**

Composition of the formulation X5 EG2

Table : 14

| **INGREDIENTS** | **X-5 EG-2** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 122.2 |
| MCC (AVICEL 102) | 102.4 |
| HPMC5cps | 14.1 |
| Water | q.s |
| HPMC K100M | 30.5 |
| Mg.stearate | 2.84 |
| Total | 296.24 |

Procedure:

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in 3Lt RMG(for 2000tabs)
4. Prepared HPMC 5cps binder solution (Take 150 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (Up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve

9. Sifted extra granular retardant through BSS # 40 and blended with material of step8
10. Sifted extra granular lubricant through BSS # 40 and blended with material of step 9
11. Compressed the blend of Step10 into round concave shaped tablets with the help of 8mm concave shaped punches

**Formulation X7 EG1**

**WET GRANULATION**:

Table 15 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation for X-7 EG-1

Composition of the formulation X7EG1

Table :15

| **INGREDIENTS** | **X-7 EG-1** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 68.4 |
| MCC (AVICEL 102) | 186.2 |
| HPMC5cps | 10.5 |
| Water | q.s |
| HPMC K100M | 3.2 |
| Mg.stearate | 2.4 |
| Total | 295.8 |

Procedure:

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in 3Lt RMG(for 2000tabs)

4. Prepared HPMC 5cps binder solution (Take 150 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition of above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (Up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular retardant through BSS # 40 and blended with material of Step8
10. Sifted extra granular lubricant through BSS # 40 and blended with material of Step9
11. Compressed the blend of Step10 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X8**

**WET GRANULATION**:

Table 16 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation for X-8

Composition of the formulation X8

Table :16

| **INGREDIENTS** | **X-8** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 204.3 |
| MCC (AVICEL 102) | 32.5 |
| HPMC 5cps | 16.6 |
| Water | q.s |
| HPMC K100M | 19.2 |
| Mg.stearate | 2.02 |
| Total | 300.22 |

Procedure:

1. Weighed all ingredients accurately

2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in 3Lt RMG(for 2000tabs)
4. Prepared HPMC 5cps binder solution (Take 150 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition of binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (up to LOD<2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular retardant through BSS # 40 and blended with material of Step8
10. Sifted extra granular lubricant through BSS # 40 and blended with material of Step9

Compressed the blend of Step10 into round concave shaped tablets with the help of 8 mm concave shaped punches

**Formulation X9**

**WET GRANULATION :**

Table 17 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation for X-9

Compositions of the formulation X9

Table : 17

| **INGREDIENTS** | **X-9** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 209.2 |
| MCC (AVICEL 102) | 31.1 |
| HPMC5cps | 16.4 |
| Water | q.s |
| HPMC K100M | 18.2 |
| Mg.stearate | 2.02 |
| Total | 302.52 |

Procedure:

1. Weighed all ingredients accurately
2. Sifted metoprololsuccinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in 3Lt RMG(for 2000tabs)
4. Prepared HPMC 5cps binder solution (Take 150 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition of above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular retardant through BSS # 40 and blended with material of Step8
10. Sifted extra granular lubricant through BSS # 40 and blended with material of Step9
11. Compressed the blend of Step10 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X8 T1**

**WET GRANULATION**:

Table 18 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation X-8 Trial-1

Composition of the formulation X8 T1

Table :18

| INGREDIENTS | X-8 trial-1 |
|---|---|
| | mg/tab |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 207.7 |
| MCC (AVICEL 102) | 33.2 |
| HPMC 5cps | 15.4 |
| Water | q.s |
| HPMC K100M | 19.4 |
| Mg.stearate | 2.02 |
| Total | 303.02 |

**Procedure:**

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in 3Lt RMG(for 2000tabs)
4. Prepared HPMC 5cps binder solution (Take 150 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (Up to LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular retardant through BSS # 40 and blended with material of Step8
10. Sifted extra granular lubricant through BSS # 40 and blended with material of Step9
11. Compressed the blend of Step10 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X8 T2**

**WET GRANULATION :**

Table 19 gives details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation X-8 Trail-2

Composition of the formulation X8 T2

Table: 19

| **INGREDIENTS** | **X-8 trial-2** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 208.2 |
| MCC (AVICEL 102) | 31.1 |
| HPMC5cps | 16.4 |
| Water | q.s |
| HPMC K100M | 18.2 |
| Mg.stearate | 2.02 |
| Total | 301.52 |

**Procedure:**

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in 3Lt RMG(for 2000tabs)
4. Prepared HPMC 5cps binder solution (Take 150 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution added to dry mixed blend in 2-3 min
6. Wet granules are formed by the addition of above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C for 45 minutes. (upto LOD <2%)
8. Sifted dried granules through BSS # 25 sieve
9. Sifted extra granular retardant through BSS # 40 and blended with material of Step8

10. Sifted extra granular lubricant through BSS # 40 and blended with material of Step9
11. Compressed the blend of Step10 into round concave shaped tablets with the help of 8mm concave shaped punches.

**Formulation X10**

**WET GRANULATION:**

Table 20 gives the details of ingredients used in composition preparation of metoprolol succinate tablets by wet granulation for X-10

Composition of the formulation X10

Table: 20

| **INGREDIENTS** | **X-10** |
|---|---|
| | **mg/tab** |
| Metoprolol succinate | 25.6 |
| Xanthan gum | 207.6 |
| MCC (AVICEL 102) | 32.3 |
| HPMC5cps | 16.5 |
| Water | q.s |
| HPMC K100M | 19.1 |
| Mg.stearate | 2.02 |
| Total | 304.4 |

**Procedure:**

1. Weighed all ingredients accurately
2. Sifted metoprolol succinate, polymer, diluents through #40 sieve
3. That step 2 material is dry mixed for 20 min in FBC
4. Prepared HPMC 5cps binder solution (Take 400 ml of water add HPMC 5cps slowly with continuous stirring)
5. That step 4 binder solution slowly sprayed in blend with the help of top spray at the conditions
6. Wet granules are formed by the addition of above binder solution
7. Wet granules of Step 6 were dried at $60^{o}$ C. (up to LOD<2%)
8. Sifted dried granules through BSS # 25 sieve

9. Sifted extra granular retardant through BSS # 40 and blended with material of Step8
10. Sifted extra granular lubricant through BSS # 40 and blended with material of Step9
11. Compressed the blend of Step10 into round concave shaped tablets with the help of 8mm concave shaped punches.

## 6.5.EVALUATION OF MATRIX TABLETS:

The prepared matrix tablets were evaluated for General appearance, thickness, hardness, weight variation, friability and drug content.

### General appearance:

The tablets prepared were white, round, spherical shape. They were smooth, uniform and free from cracking and chipping

### Hardness test

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The permissible limit for hardness is 4-12kg/cm$^2$. The hardness was tested using Monsanto tester. "Hardness factor", the average of the ten determinations was determined and reported. The results are shown in the table: 24

### Uniformity of weight (Weight variation test):

This is an important In-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight. 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The

percentage difference in the weight variation should be within the permissible limits (7.5%). The percent deviation was calculated using the following formula**.** The limits are mentioned in the below table as per Indian pharmacopoeia (I.P). The results are shown in the table: 24

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

| **Average weight** | **Percent difference** |
|---|---|
| 130 mg or less | 10 |
| More than 130 mg but less than 324 mg | 7.5 |
| More than 324 mg | 5 |

**Friability test:**

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This In-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Five tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula The results are shown in the table: 24

$$\mathbf{(W_1 - W_2)/W_1 \times 100}$$

Where,

$W_1$ = weight of the tablets before test

$W_2$ = weight of the tablets after test

**Content of active ingredient**

To ensure the consistency of dosage units, each unit in a batch should have active substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of an active substance in each dosage unit.

Ten tablets from each formulation were powdered. The powder equivalent to 50 mg of metoprolol was weighed and dissolved in 5 ml of water and 60 ml of methanol in 200 ml standard flask Shaken for 30 min and then made up with 0.1N Hcl and then centrifuge . 5 ml of this solution in 50 ml standard flask was made up with mobile phase AS per procedure given below generally; the drug content in any formulation should fall within the limit of 90 – 110%. Ref USP vol 3

**6.6 ESTIMATION OF METOPROLOL SUCCINATE:**

**Mobile Phase :**

(1) Mix pH 3.0 buffer solution and Acetonitrile in the ratio of 75 : 25 respectively.

(2) Degas in a sonicator for about 10 minutes.

**Standard Preparation:**

Transfer about 12 mg of Metoprolol succinate working standard, accurately weighed to a 100 ml volumetric flask ,and add 50 ml of pH 6.8 phosphate buffer, dissolve in and dilute to volume with mobile phase.
Standard stock solution into a 50 ml volumetric flask and

(1) Pipette 1 ml of the above Standard stock solution into a 10 ml volumetric flask and dilute to volume with dissolution medium pH6.8 phosphate buffer and mix.

**Chromatographic System :**

(1) The liquid Chromatographic system is equipped with a 280-nm UV detector.

(2) Column : 4.6-mm x 150-mm column that contains 5 µm packing octylsilane

chemically bonded to porous silica or ceramic micro-particles,(4.6-mm x 150-mm, Xterra RP8, 5µm or equivalent).

(3) Column temperature : Ambient

(4) Flow rate : 1.0 ml per minute.

**System suitability:**

(1) Inject 40 µL portion of the Standard preparation into chromatographic system for five times, record the record the chromotogram and measure the response for major peak.

(a) Tailing factor for Metoprolol Succinate peak should be not more than 2.0

(b) The relative standard deviation for peak areas of Metoprolol Succinate for five

Replicate injections should be not more than 2.0 %

**Procedure:**

Inject 40 µL portion of the dissolution medium as blank, standard preparation for five times, test preparation into the chromatograph, record the chromatogram and measure the responses for major peaks

**Calculations:**

Quantity of Metoprolol Succinate dissolved in n th time interval as % of labeled amount.

$$Dn = \frac{An \times Ws \times 5 \times P \times 500 \times 100}{As \times 100 \times 100 \times 100 \times L}$$

Where:-

An = Peak area of Metoprolol Succinate for Test preparation, in n th time interval.

AS = Peak area of Metoprolol Succinate for Standard preparation.

P = Potency of Metoprolol Succinate Standard calculated as Metoprolol Succinate.

L = Labeled amount of Metoprolol Succinate in mg, per Tablet.

**Calculation of Correction factors:**

% of Metoprolol succinate present in sample volume after 1st time interval,

$$F_1 = (D_1 / 900)x10$$

% of Metoprolol succinate present in sample volume after 2nd time interval,

$$F_2 = (D_2 / 900)x10$$

% of Metoprolol succinate present in sample volume after 3rd time interval,

$$F_3 = (D_3 / 900)x10$$

% of Metoprololsucciante present in sampled volume after 4th time interval,

$$F_4 = (D_4 / 900)\ x10$$

**Calculation of Corrected results:**

For 1st time interval = $D_1$ (No correction required).

For 2nd time interval = $D_2 + F_1$

For 3rd time interval = $D_3 + F_1 + F_2$

For 4th time interval = $D_4 + F_1 + F_2 + F_3$

**6.7 ASSAY:**

**Reagents:**

**Preparation Buffer solution:**

(1) Dissolve about 6.9 g of Sodium dihydrogen phosphate monohydrate in 1000 ml of Milli-Q-water and mix.

(2) Adjust the pH of the solution to 3.0 with Orthophosphoric acid.

(3) Filter the above solution through 0.45µm DuraporeHydrophyllic membrane filter.

**Mobile phase:**

Mix Buffer and Acetonitrile in the ratio of 75: 25.Degas in a sonicator for 10 minutes.

**Standard Preparation:**

(1) Transfer about 95 mg of Metoprolol succinate reference standard or working standard,

Accurately weighed to a 100- ml volumetric flask. Dissolve and dilute to volume with mobile phase and mix.

(2) Pipette 5 ml of above solution into a 100 ml volumetric flask, dilute to volume with Mobile phase and mix.

(3) Filter through 0.45µm M D I Nylol-66 membrane filter

**Test Preparation:**

(1) Transfer an accurately weighed amount of 260 mg of matrix tablet crushed powder in to a 100 ml volumetric flask

(2) Add about 5 ml of water shake the flask for 2 minutes to disintegrate, and add 30 ml of ethanol and shake for 30 minutes on rotary shaker and add about 40 ml of 0.1N Hydrochloric acid and keep on a rotary shaker for 30 minutes.

(3) Dilute to volume with 0.1N Hydrochloric acid and mix.

(4) Centrifuge the above solution with cap at 4000 rpm for about 10 minutes.

(5) Pipette 5 ml of the above clear centrifugate into a 50 ml volumetric flask, dilute to volume with mobile phase and mix.

(6) Filter about 2 ml through 0.45µm membrane filter .

**Chromatographic System:**

(1) Detector: Liquid Chromatographic system equipped with UV Visible detector at 280 nm

(2) Column: 4.6-mm x 150mm column that contains packing octylsilane

Chemically bonded to porous silica, 3 to 10 µm in diameter.(4.6-mm x 150-mm, Xterra RP 8, 5µ or equivalent).

(3) Column temperature: Ambient

(4) Flow rate: 0.8 ml per minute.

**System suitability:**

(1) Inject 40 µL portion of the Standard preparation into chromatographic system for five times, record the record the chromatogram and measure the response for major peak.

(2) Tailing factor for Metoprolol Succinate peak should be not more than 2.0

(3) The relative standard deviation for peak areas of Metoprolol Succinate for five

Replicate injections should be not more than 2.0 %

**Procedure:**

Inject 40µL portion of the mobile phase and test preparation into the chromatograph,

Record the chromatogram and measure the peaks response.

**Calculations:**

Quantity of Metoprolol succinate present in portion of ER Tablet as % of labeled amount

$$= \frac{A \times Ws \times 5 \times P \times 500 \times 100 \times 1000 \times 100}{\text{---------------------------------------------------------}}$$

A = Peak area of Metoprolol succinate for test preparation. S =

P = Potency of Metoprolol succinate Standard calculated as Metoprolol succinate.

Wt = Weight of pellets taken, in "mg" for test preparation.

L = Labeled claim of metoprolol succinate per gram.

**6.8.In-vitro drug release studies:**

In-vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900 ml of dissolution medium maintained at 37±0.5°C for 20 hrs, at 100 rpm, pH 6.8 ±0.2 phosphate buffer as dissolution medium.

Sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and concentration of drug in each sample was analyzed by HPLC at 280 nm and cumulative percent drug release was calculated. The study was performed in triplicate .The commercial Toprol XL tablets were used as the reference formulation, and were also subjected to *In-vitro* drug release studies

The results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1. Log cumulative percent drug remaining versus time (firstorder kinetic model)

2. Cumulative percent drug release versus square root of time (Higuchis model)

3. Cumulative percent drug release versus time (zero order kinetic model)

4. Log cumulative Percent Drug released versus log time (korsmeyers model)

**Drug release kinetics-model fitting of the dissolution Data:**

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Nowadays the pharmaceutical industry and the registration authorities focus on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analytical definitions of the Q (t) function are commonly used such as zero order, first order, Higuchi, korsmeyers models. Other release parameters, such as dissolution time ($t_{x\%}$), dissolution efficacy (ED), difference factor ($f_1$), similarity factor ($f_2$) can be used to characterize drug dissolution / release profile.

**Zero-order kinetics :**

A zero-order release would be predicted by the following equation.

$$\mathbf{At = A_o - K_o t} \qquad \text{.....} \ 1$$

Where

At = Drug release at time t

$A_o$ = Initial drug concentration

$K_o$ = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to $k_o$.

**Use:**

This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in case of some transderrmal systems etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

**First-order kinetics:**

A first order release would be predicted by the following equation.

$$\textbf{Log C} = \textbf{Log Co} - \textbf{K}_t / \textbf{2.303} \qquad 2$$

Where

C = Amount of drug remained at time t

$C_o$ = Initial amount of drug

K = First-order rate constant

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line indicating the release follows first-order kinetics, the constant k can be obtained by multiplying 2.303 with slope values

**Use:**

The pharmaceutical dosage forms containing water-soluble drugs in porous matrices, follows this type of dissolution profile. The release of the drug is proportional to the amount of drug remaining in its interior so that the amount of drug release by unit of time diminishes

**Higuchimodel:**

Drug release from the matrix devices by diffusion has been described by following Higuchis classical diffusion equation.

$$Q = [DE/\tau(2A - ECs)\, C_{st}] \qquad \ldots\ldots\ldots\ldots\ldots\ 3$$

Where

Q = Amount of drug release at time t

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

$C_s$ = The solubility of the drug in the matrix

E = Porosity of the matrix

T = Time in hrs at which q is the amount of drug is release

Equation-3 may be simplified if one assumes that D, Cs and A are constant. Then equation-3 becomes

$$Q = K_t{}^{1/2}$$

When the data is plotted according to equation-4 i.e. cumulative drug release versus Square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to k.

**Use:**

The relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in case of some water soluble drugs.

**K** In order to understand the mode of release of drug from swell able matrices, the data were fitted to the following equation

$$\mathbf{M_t / M_{\acute{a}} = Kt^n}$$

Where,

$M_t / M_{\acute{a}}$ = The fraction of drug released at time 't'

K = Constant incorporating the structural and geometrical Characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of release.

The above equation can be simplified by applying log on both sides we get

$$\mathbf{Log\ M_t / M_{\acute{a}} = Log\ K + n\ Log\ t}$$

When the data is plotted as a log of drug released versus log time, yields a straight line with a slope equal to n and the k can be obtained from y- intercept.

The value of n for a cylinder is <0.45 for Fickian release, > 0.45 and < 0.89 for non-Fickian release, 0.89 for the case 2 release and > 0.89 for super case2 type release.The results are shown in the table 25.

## 6.9 DISSOLUTION:

### a. Selection of method:

Metoprolol succinate was formulated by using three methods namely direct compression, dry granulation and wet granulation.

In these three methods direct and dry granulation tablet surface was not smooth sticking problem was there, in wet granulation tablet no sticking problem was there so I selected wet granulation.

**b. Selection of polymer concentation:**

Metoprolol succinate formulated by using in 4 different concentrations of xanthan gum i,e 30%,35%,50%,70%(X-1A, X-2, X-3, X-4)

## 6.10.STABILITY STUDIES

Optimized formulation was charged for two months as accelerated stability conditions at $40^0$C/75% RH. The samples kept at $40^0$C/75% RH were compared with control samples for every month. In-vitro evaluation, assay, physical parameters were compared. Those results were as follows in the table 43 & 44.

# RESULTS AND DISSCUSIONS

### 7.1 Fourier Transform Infrared Spectroscopy:

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the polymer. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quanta of potassium bromide. About 100 mg of this mixture was compressed to from a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned from 4000 to 400 $cm^{-1}$ in a Shimadzu FTIR 8400 Spectrophotometer. The IR spectrum of the physical mixture was done to detect any appearance or disappearance of peaks.

**Fig.7:FTIR OF METOPROLOL SUCCINATE + STD+ HPMC**

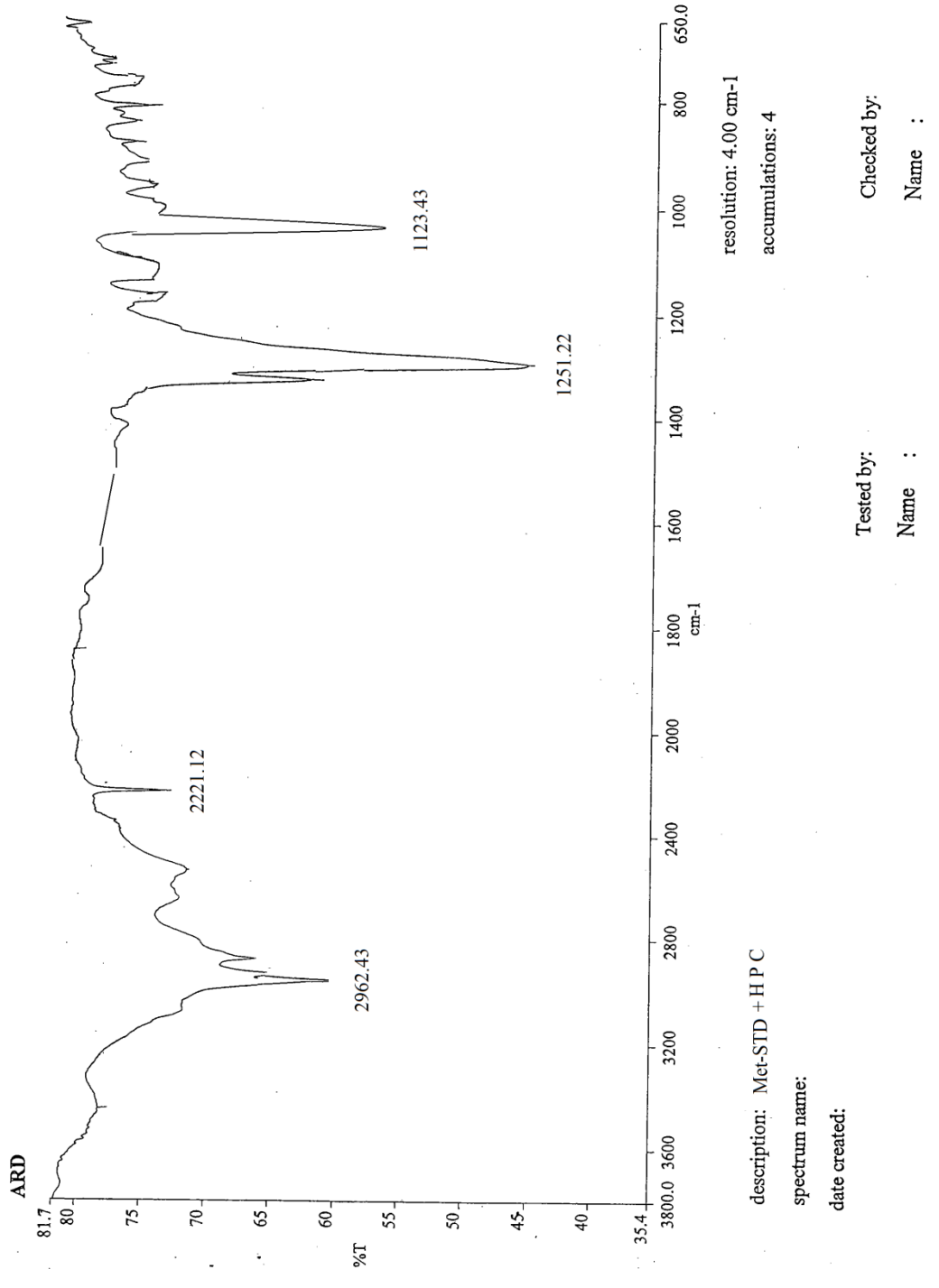
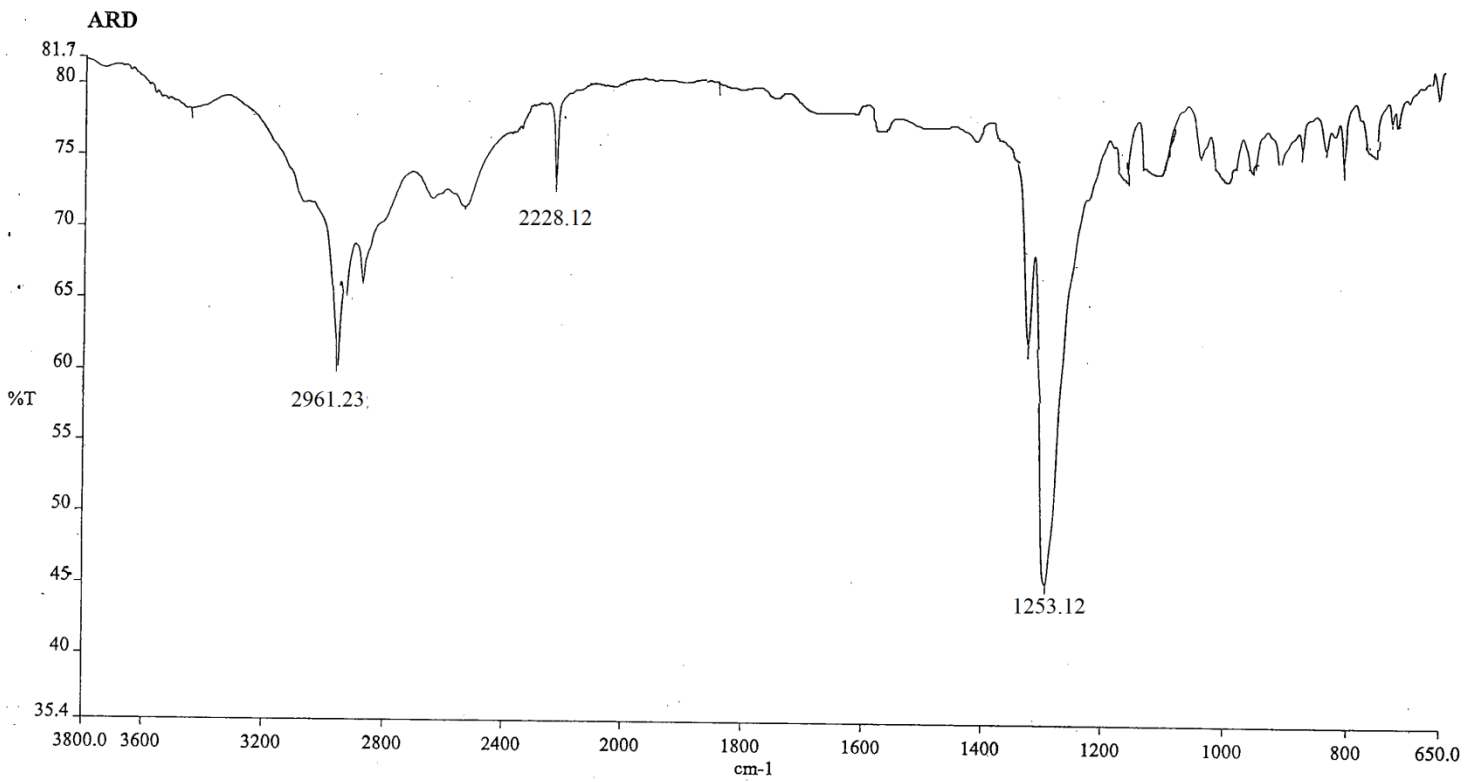



**Fig. 8: FTIR OF METOPROLOL SUCCINATE +STD +HPMC K 100M**

**Fig.9 :FTIR OF METOPROLOL SUCCINATE +STANDARD**




description: Met-STD

spectrum name:

date created:

resolution: 4.00 cm-1

accumulations: 4

Tested by:

Name :

Checked by:

Name :

Fig .10: FTIR OF METOPROLOL SUCCINATE +HPMC


description: Met+PropylMethylcellulose

spectrum name:

date created:

resolution: 4.00 cm-1

accumulations: 4

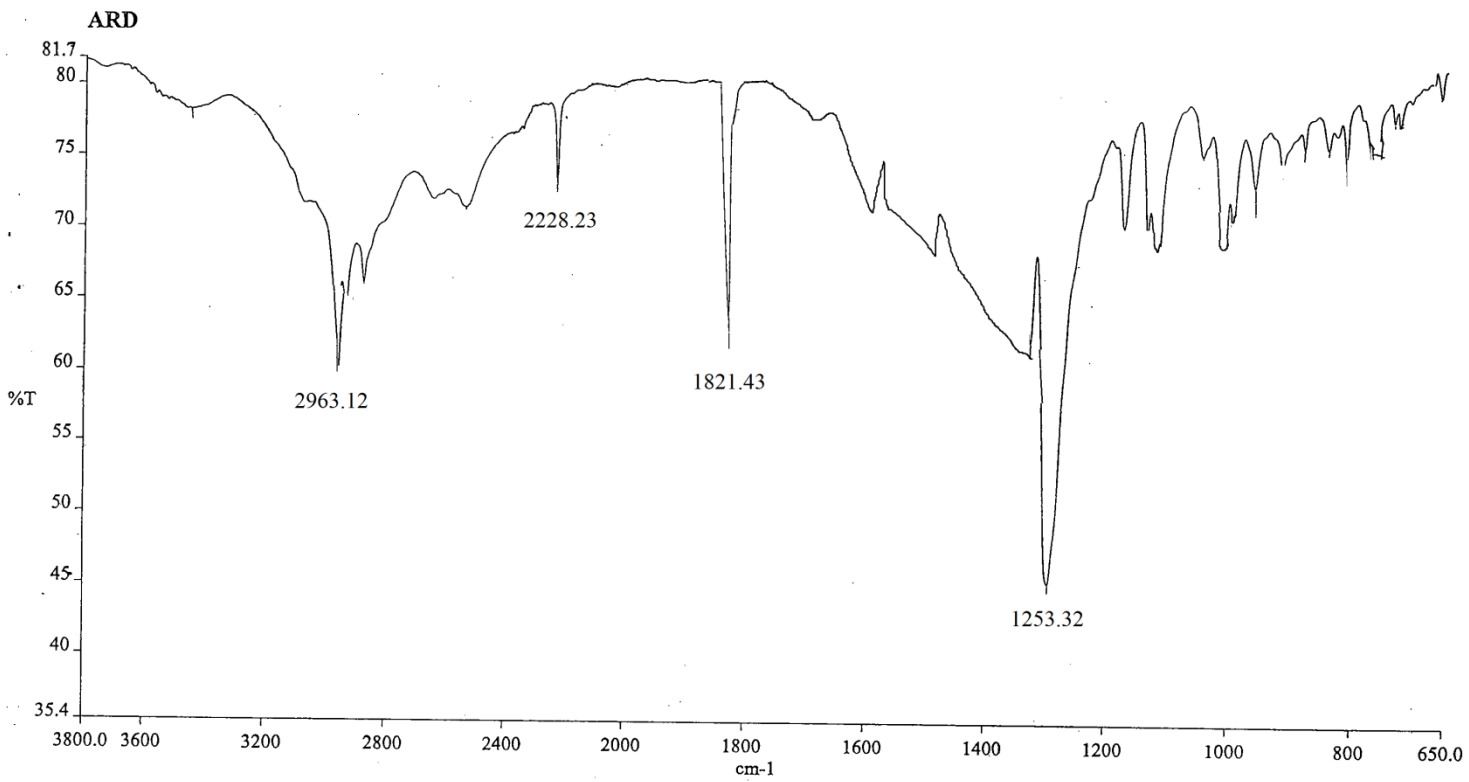
Tested by:

Name :

Checked by:

Name :

FIG .11: FTIR OF METOPROLOL SUCCINATE +MCC




description: Met+Methyl Cellulose

spectrum name:

date created:

resolution: 4.00 cm-1

accumulations: 4

Tested by:

Name :

Checked by:

Name :

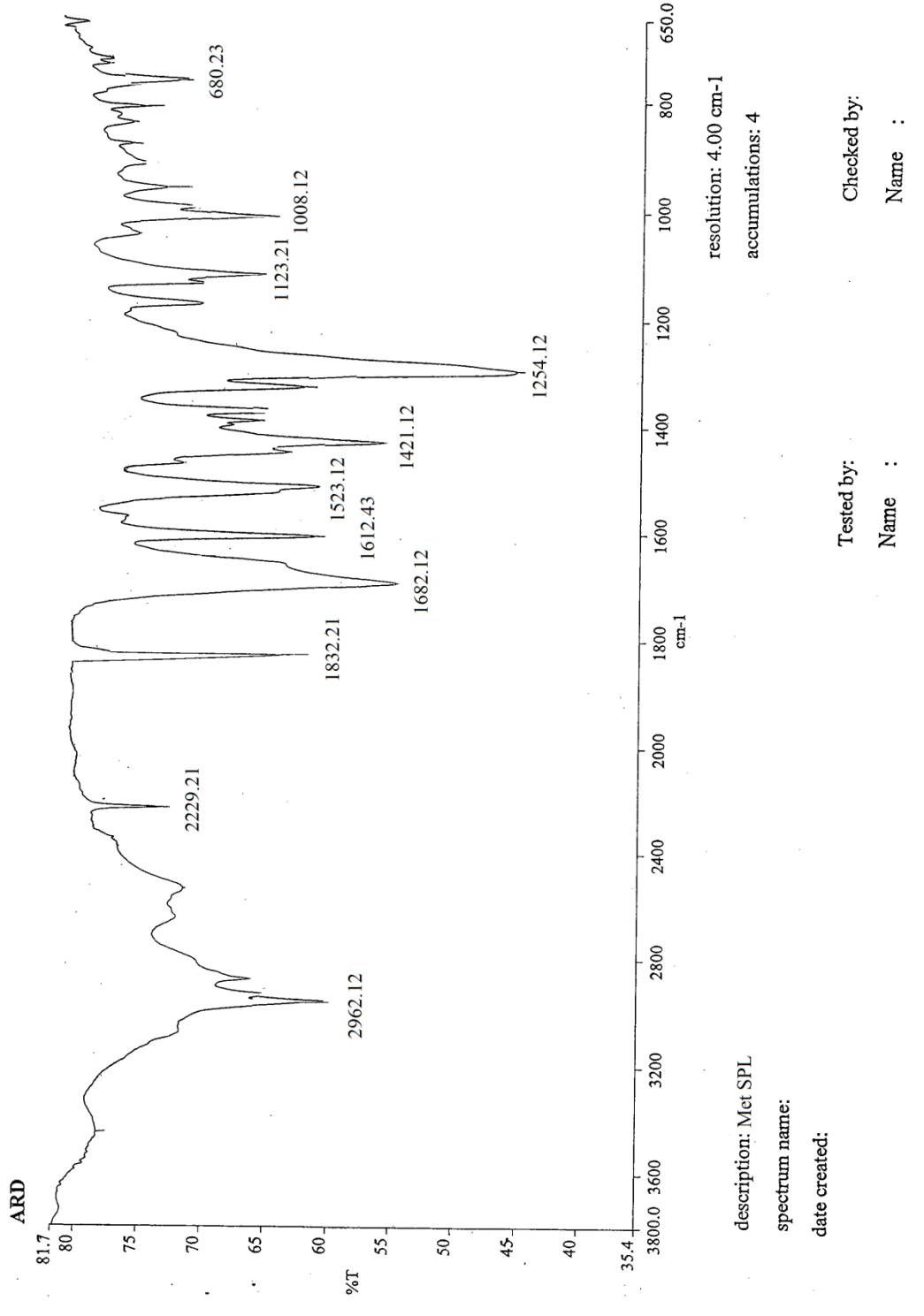



**Fig .12:FTIR METOPROLOL SUCCINATE SAMPLE**

## 7.2 PREFORMULATION RESULTS:

**Table: 22**

| Formulation | Bulk density (gm/ ml) | Tapped density ( gm/ ml) | Compressibility index ( %) | Hausner's ratio |
|---|---|---|---|---|
| X1A | 0.350 | 0.384 | 7.69 | 1.075 |
| X1B | 0.344 | 0.352 | 5.18 | 1.065 |
| X1C | 0.372 | 0.345 | 6.32 | 1.075 |
| X2 | 0.435 | 0.376 | 8.03 | 1.082 |
| X3 | 0.461 | 0.377 | 9.23 | 1.064 |
| X4 | 0.365 | 0.354 | 7.018.65 | 1.076 |
| X5 | 0.485 | 0.363 | 8.06 | 1.054 |
| X6 | 0.431 | 0.371 | 5.62 | 1.062 |
| X7 | 0.421 | 0.363 | 7.18 | 1.077 |
| X5 EG1 | 0.370 | 0.374 | 5.17 | 1.068 |
| X5 EG2 | 0.352 | 0.383 | 6.85 | 1.056 |
| X7 EG1 | 0.361 | 0.372 | 6.58 | 1.071 |
| X8 | 0.352 | 0.384 | 8.08 | 1.059 |
| X9 | 0.360 | 0.3654 | 6.62 | 1.063 |
| X8 T1 | 0.352 | 0.387 | 8.17 | 1.062 |
| X8 T2 | 0.432 | 0.386 | 9.98 | 1.075 |
| X10 | 0362 | 0.378 | 7.45 | 1.065 |

**7.3 Flow properties of API**

**Table 23:**

| S.NO | W (gm) | $V_0$ ( ml) | V ( ml) | Bulk density (gm/ ml) | Tapped density (gm/ ml) | Compressibility index* $[1-V/V_0] *100$ | Hausner' s Ratio# [T.D/B.D] |
|---|---|---|---|---|---|---|---|
| 1 | 20.00 | 56 | 52 | 0.357 | 0.384 | 7.69 | 1.075 |
| 2 | 20.00 | 57 | 53 | 0.350 | 0.377 | 7.01 | 1.076 |
| 3 | 20.00 | 58 | 55 | 0.344 | 0.363 | 5.17 | 1.05 |
| Avg. | 20.00 | 57 | 53.3 | 0.350 | 0.374 | 6.62 | 1.06 |

**7.4 Evaluation of Matrix Tablets**

**TABLE 24:**

| Formulations | Weight(mg) | Thickness(mm) | Hardness(kp) | Friability(%) | Assay(%) |
|---|---|---|---|---|---|
| X1A | 297 | 4.3 -4.4 | 6.8 | 1.08 | 100.2 |
| X1B | 297.9 | 4.3 -4.4 | 6.8 | 1.02 | 101 |
| X1C | 297.2 | 4.2 -4.3 | 12.2 | 0.09 | 99.63 |
| X2 | 295.9 | 4.3 -4.4 | 11 | 0.07 | 101.2 |
| X3 | 296.7 | 4.4 -4.5 | 9.6 | 1.02 | 102 |
| X4 | 299.9 | 4.5 -4.6 | 8.5 | 1.06 | 100.1 |
| X6 | 297 | 4.3 -4.4 | 7.5 | 1.03 | 99.8 |
| X7 | 296.4 | 4.3 -4.4 | 9.6 | 1.02 | 102.2 |
| X5 EG1 | 299.5 | 4.4 -4.5 | 6 | 1.08 | 99.23 |
| X5 EG2 | 296.24 | 4.4 -4.5 | 5.7 | 1.05 | 100.4 |
| X7 EG1 | 295.8 | 4.3 -4.4 | 6.9 | 1.02 | 100.4 |
| X8 | 312.22 | 4.6 -4.7 | 7.8 | 0.09 | 100.6 |
| X9 | 311.52 | 4.5 -4.6 | 6.8 | 1.02 | 101.7 |
| X8 T1 | 312.02 | 4.9 -5.0 | 8.9 | 1.07 | 102.2 |
| X8 T2 | 311.52 | 4.8 -4.9 | 7.6 | 1.05 | 100.3 |
| X10 | 312.4 | 4.4 -4.5 | 5.5 | 1.06 | 100.1 |

## 7.5 ESTIMATION OF RELEASE MECHANISMS BY MATHAMETICAL MODELS

The rate of release of metoprolol succinate was calculated using data fitting method for X8 formulation and results are as follows

**Table 25: Release mechanism by mathematical models**

| Release mechanism | Values |
|---|---|
| Zero – order(r) | 0.9349 |
| First order(r) | 0.9987 |
| Higuchi(r) | 0.9943 |
| Peppas(n) | 0.6845 |

**7.6 Dissolution**

**In-vitro Evaluation:**

Table 26 : % Cumulative drug release of metoprolol succinate extended release matrix tablets at different concentrations of xanthan gum

| **Time in hrs** | **Cumulative %drug release** | | | | |
|---|---|---|---|---|---|
| | **X-1A** | **X-2** | **X-3** | **X-4** | **Marketed sample** |
| 1hr | 20 | 18 | 13 | 11 | 10 |
| 4hr | 49 | 42 | 34 | 31 | 29 |
| 8hr | 75 | 64 | 56 | 51 | 49 |
| 20hr | 102 | 92 | 88 | 82 | 84 |

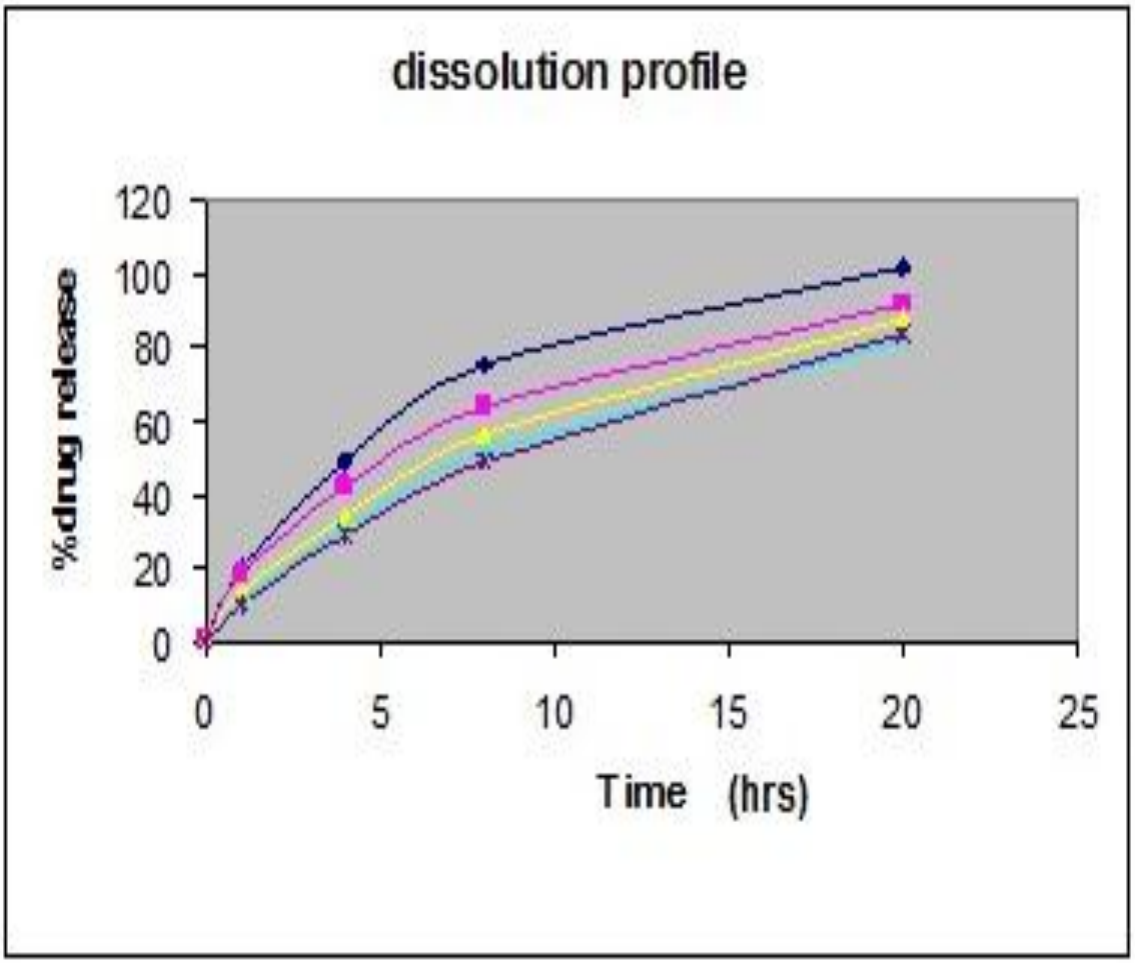



Fig 13 shows % Cumulative drug release of metoprolol succinate from

From the above results for the formulation of matrix formulation , 50% and 70% xanthan gum formula are choosen, because that two formulations results nearer to marketed sample.

**Effect of Extra Granular:**

**Table 27:** % Cumulative drug release of Metoprolol succinate extended release matrix tablets at different extra granular concentrations of below formulations.

| **Time in hrs** | **Cumulative %drug release** | | | | | |
|---|---|---|---|---|---|---|
| | **X-5** | **X-5 EG-1** | **X-5 EG-2** | **X-7** | **X-7 EG-1** | **Marketed sample** |
| **1** | 20 | 18 | 13 | 15 | 14 | 10 |
| **4** | 49 | 42 | 34 | 38 | 36 | 29 |
| **8** | 75 | 64 | 56 | 62 | 60 | 49 |
| **20** | 102 | 92 | 88 | 100 | 97 | 84 |

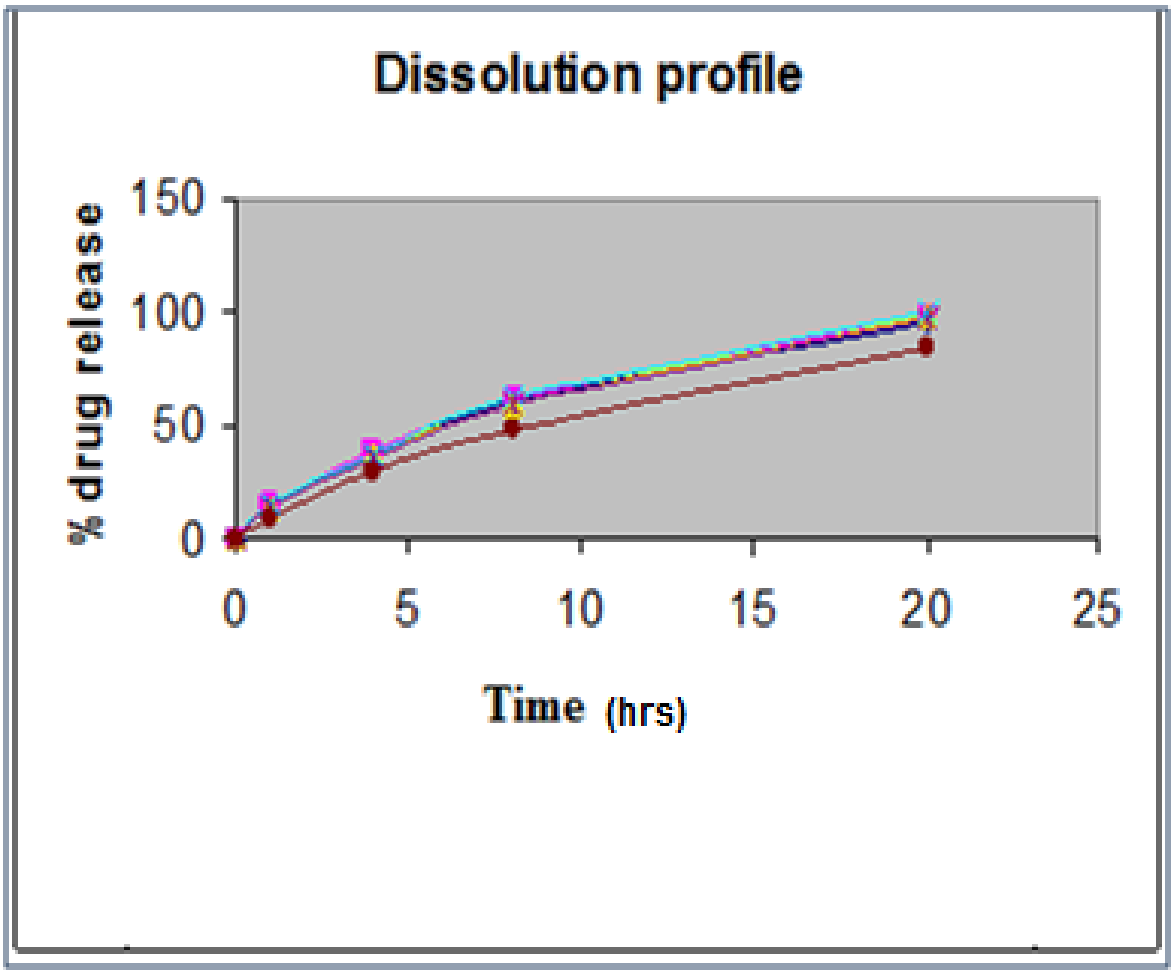



Fig 14 shows% Cumulative drug release of metoprolol succinate from

From the above results conclusion is extra granular concentration and dissolution profile is directly proportional so, in the next trials extra granular is added.

**Effect of particle size:**

Table 28 : % Cumulative drug release of Metoprolol succinate extended release matrix tablets at different particle size of the granules.

| **Time** | **Cumulative %drug release** | |
|---|---|---|
| | **X-6** | **Marketed sample** |
| | #25 | |
| 1 | 16 | 10 |
| 4 | 41 | 29 |
| 8 | 66 | 49 |
| 20 | 103 | 84 |

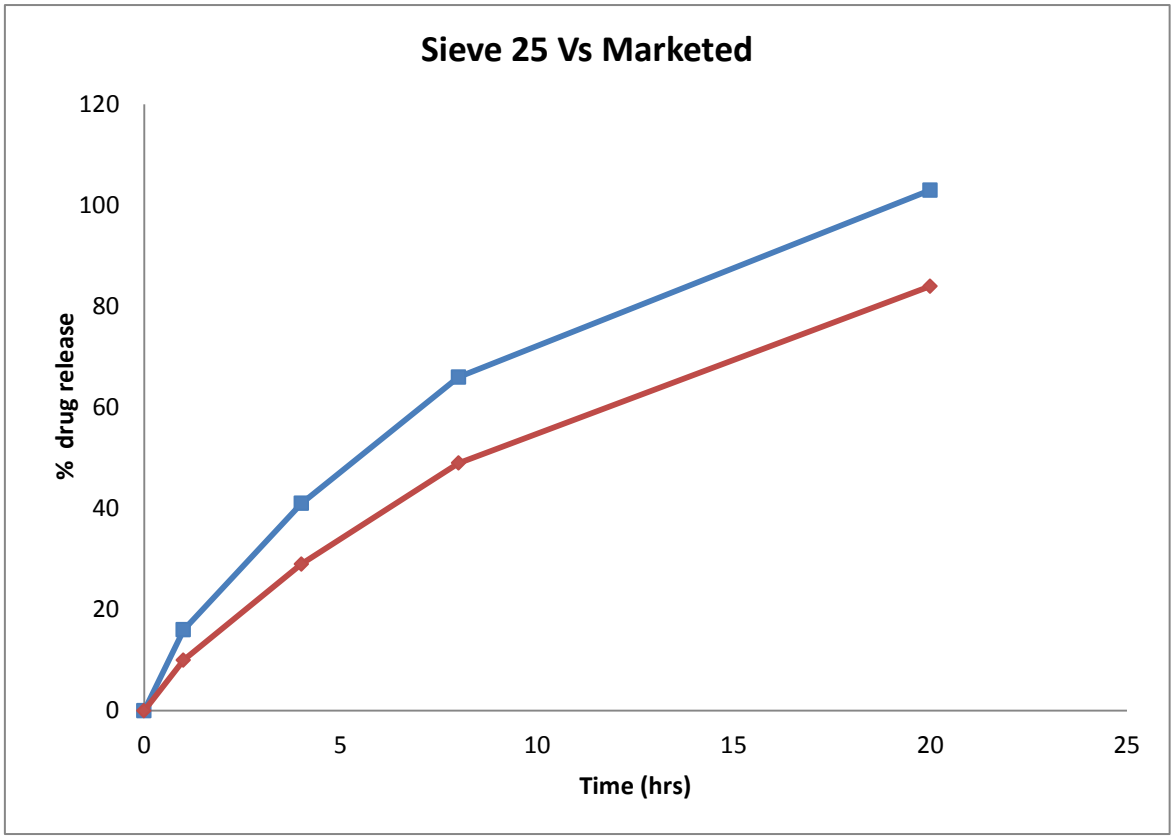



Fig :15 shows % Cumulative drug release of Metoprolol succinate from

From the above dissolution result particle size of the formulation does not vary the dissolution result, so in this #25 mesh is selected for all the formulations.

**Optimization of formula:**

Table 29 : % Cumulative drug release of Metoprolol succinate extended release matrix tablets with extra granulation.

| Time in hrs | Cumulative %drug release | | |
|---|---|---|---|
| | **X-8** | **X-9** | **Marketed sample** |
| 1 | 12 | 12 | 10 |
| 4 | 33 | 32 | 29 |
| 8 | 54 | 52 | 49 |
| 20 | 90 | 88 | 84 |

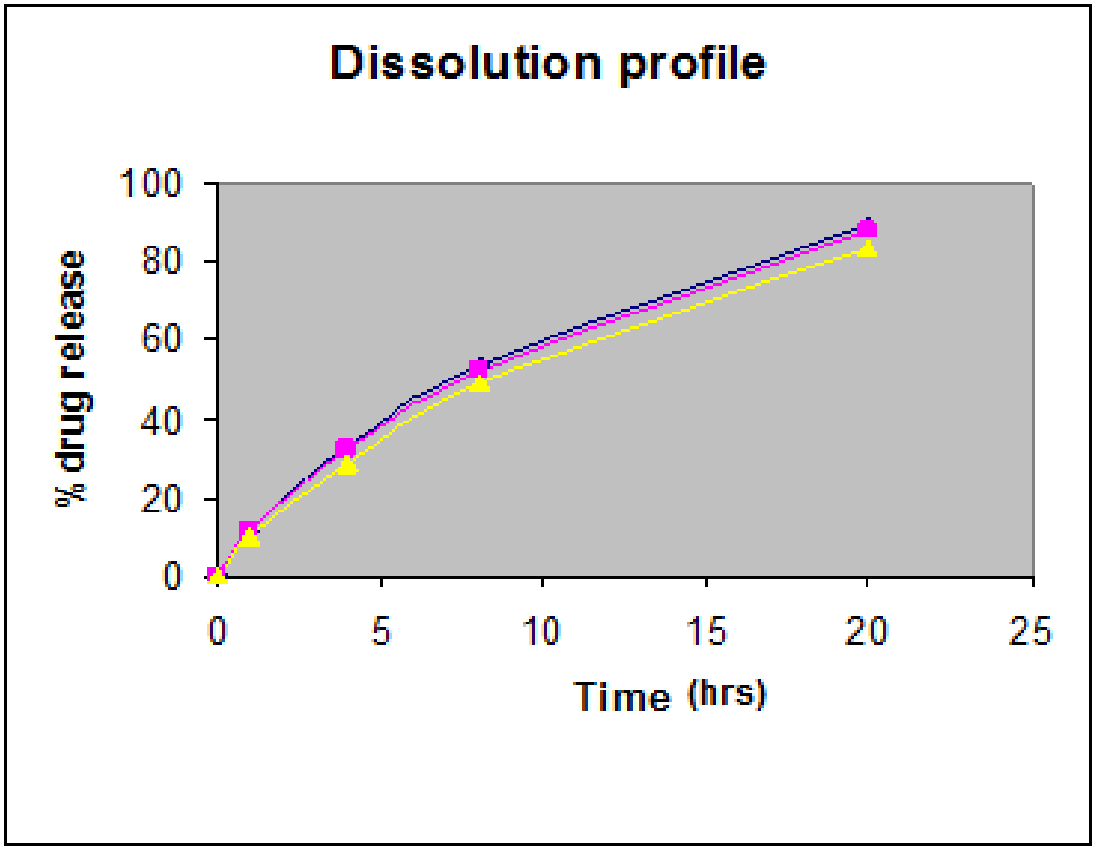



Fig 15 shows % Cumulative drug release of Metoprolol succinate from


From the above dissolution results X-8,X-9 formulas matches with marketed sample so in this X-8 formula taken and seen the reproducibility of the batch.

**Reproducibility batches:**

Table 30: % Cumulative drug release of metoprolol succinate extended release matrix tablets for reproducibility batches

| Time in hrs | Cumulative %drug release | | |
|---|---|---|---|
| | **X-8 Trial-1** | **X-8 trial-2** | **Marketed sample** |
| 1 | 14 | 14 | 10 |
| 4 | 34 | 35 | 29 |
| 8 | 54 | 56 | 49 |
| 20 | 89 | 91 | 84 |

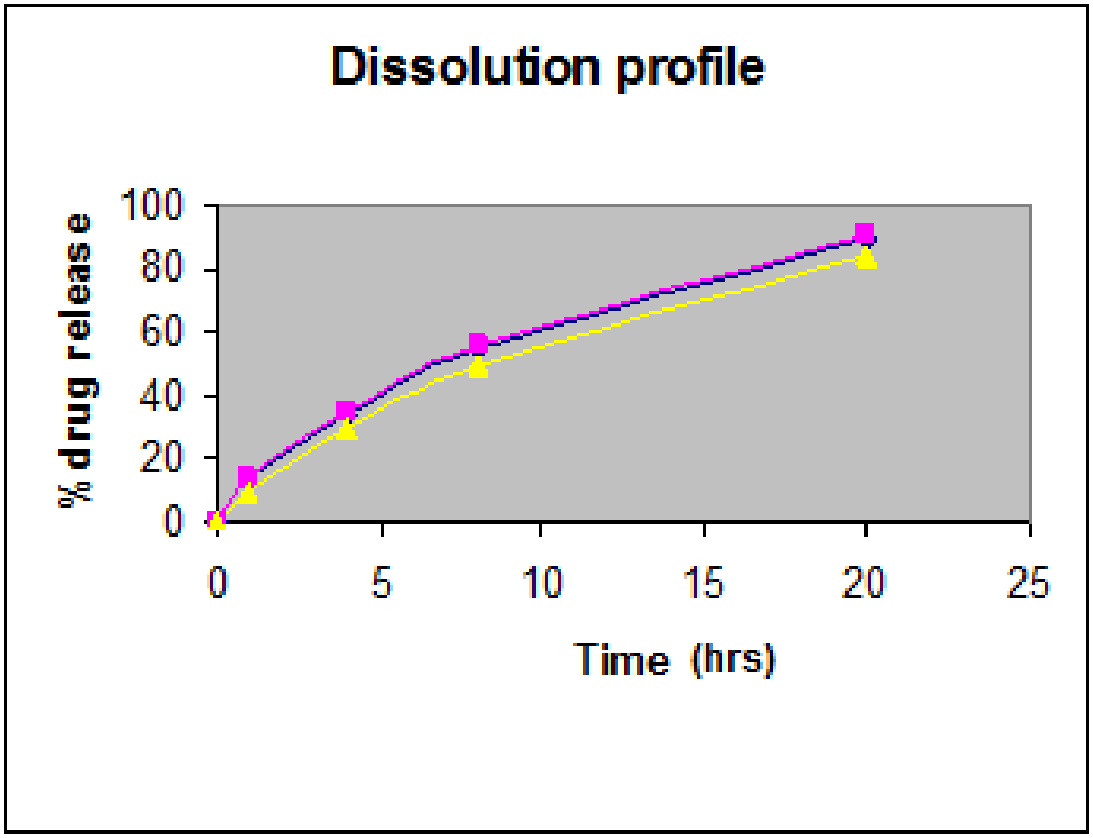
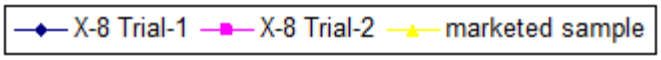



Fig 16 shows % Cumulative drug release of metoprolol succinate from




Reproducibility batches result is also very good, but in the RMG granules was very hard , at the time of shifting it has problem so , one trial in FBC with same formula was performed

**FBC batch:**

Table 31: % Cumulative drug release of metoprolol succinate extended release matrix tablets for FBC batch.

| Time | Cumulative %drug release | |
|---|---|---|
| | X-10 | Marketed sample |
| 1 | 14 | 10 |
| 4 | 34 | 29 |
| 8 | 54 | 49 |
| 20 | 85 | 84 |

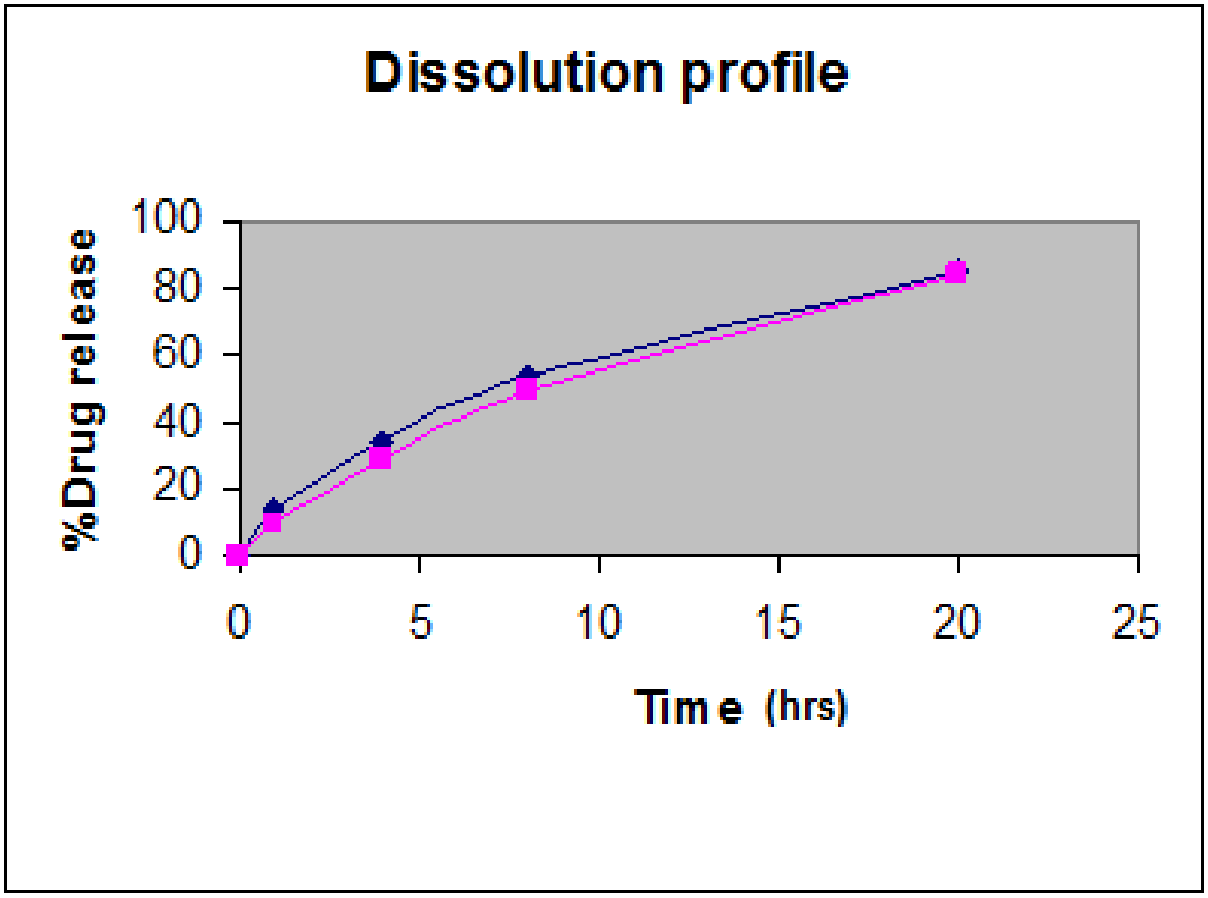



Fig 17 shows % Cumulative drug release of metoprolol succinate from

From the above FBC process results showing pharmaceutical equivalence product. And also overcome the hard granules problem faced in RMG process. This FBC process is also very easy and given a pharmaceutical equivalent product

## 7.7 Assay method validation:

1. System suitability and precision:

The standard solution prepared by using Metoprolol succinate working standards as per the test method and injected six times into HPLC system. The system suitability parameters were evaluated and found to be within the limits. The RSD for peak areas from five replicate injections of Metoprolol was found to be within limits .The RSD for peak areas from five replicate injections of Metoprolol was found to be 0.1%, and the tailing factor of Metoprolol is found to be 1.3.

Table 32: System precision and system suitability

| **Injection number** | **Metoprolol succinate** |
|---|---|
| | **ASSAY** |
| 1 | 1243450 |
| 2 | 1245626 |
| 3 | 1243983 |
| 4 | 1243172 |
| 5 | 1241181 |
| Mean | 1243482 |
| %RSD | 0.1 |

| System suitability | Observed value | Acceptance criteria |
|---|---|---|
| The tailing factor for Metoprolol | 1.3 | NMT 2.0 |

2 .Linearity:

A graph is plotted to “concentration” versus “area” in linearity section. The correlation coefficient was found to be 0.99964 for Metoprolol. From the above study it was established that the detector linearity is from 25% to 150% of the labeled amount of Metoprolol Succinate tablets.

Table 33: Linearity of detector response

| Standard concentration | Area |
|---|---|
| 25% | 298146 |
| 50% | 622976 |
| 75% | 940316 |
| 100% | 1239674 |
| 125% | 1580572 |
| 150% | 1847581 |
| Coefficient of correlation(r) | 0.999644 |

3.Specificity(placebo interference):

A study of placebo interference from excipients was conducted. Placebo interference checked by taking about 565mg of placebo in 250 ml of volumetric flask in triplicate, equivalent to about the weight of placebo as per the test method. There is no interference at RT of Metoprolol peak.

Table34 : Placebo interference

| Sample no. | %interference found |
|---|---|
| | Tablets |
| 1 | Nil |
| 2 | Nil |
| 3 | Nil |

4.Precision:

The precision of test procedure was evaluated for Metoprolol tablets by performing the assay and content uniformity as per the test method. The % relative standard deviation recovery of Metoprolol was found to be within the limits.

Table 35: Repeatability

| Sample no. | % drug recovered |
|---|---|
| 1 | 99.23 |
| 2 | 99.28 |
| 3 | 98.40 |
| 4 | 97.97 |
| 5 | 98.68 |
| 6 | 98.57 |
| 7 | 98.69 |
| 8 | 0.5 |

5.Accuracy:

A study was conducted. Drug assy was performed in triplicate by spiking with equivalent amount of Metoprolol raw material into each volumetric flask for each spike level to get the concentration of Metoprolol equivalent to 25%,50%,75%,100%,125% and 150% of the labeled amount of metoprolol as per

the test method. The average % recovery of Metoprolol was found to be within the limits.

Table 36: Accuracy

| Sample No. | Spike Level | Amount Added(Ppm) | Amount Found(Ppm) | Mean% Recovery |
|---|---|---|---|---|
| 1 | 25% | 11.875 | 11.87 | 100.16 |
| 2 | 25% | 11.875 | 12.01 | |
| 3 | 25% | 11.875 | 11.78 | |
| 4 | 50% | 23.75 | 23.64 | 99.53 |
| 5 | 50% | 23.75 | 23.81 | |
| 6 | 50% | 23.75 | 23.46 | |
| 7 | 75% | 35.625 | 35.62 | 100.01 |
| 8 | 75% | 35.625 | 35.80 | |
| 9 | 75% | 35.625 | 35.45 | |
| 10 | 100% | 47.5 | 47.55 | 100.11 |
| 11 | 100% | 47.5 | 47.69 | |
| 12 | 100% | 47.5 | 47.50 | |
| 13 | 125% | 59.375 | 59.20 | 99.71 |
| 14 | 125% | 59.375 | 59.08 | |
| 15 | 125% | 59.375 | 59.32 | |
| 16 | 150% | 71.25 | 71.12 | 99.82 |
| 17 | 150% | 71.25 | 71.05 | |
| 18 | 150% | 71.25 | 71.19 | |

6.Linearity of test method:

A graph is plotted to “amount of Metoprolol added” Versus “amount of Metoprolol found” in accuracy section. The correlation coefficient was found to be 0.999995. From the above study it was established that the linearity of test method is from 25% to 150% of the labeled amount of Metoprolol.

Table 37: Linearity of test method

| Spike level in % | Amount added | Amount found |
|---|---|---|
| 25% | 11.875 | 11.89 |
| 50% | 23.75 | 23.64 |
| 75% | 35.625 | 35.62 |
| 100% | 47.5 | 47.58 |
| 125% | 59.375 | 59.2 |
| 150% | 71.25 | 71.12 |

7.Ruggedness:

i) Bench top stability of standard and test preparations:

The bench top stability of Metoprolol in standard and test preparation was established over a period of about 2 days. Both standard and test preparations were stored on bench top and analyzed at Initial, 1day and 2day against a freshly prepared standard each time. The difference in %assay of standard and test preparation from initial to 2days was found to be within the limits. The standard and test preparations are stable up to 48hrs

From the above study, it was established that Metoprolol in standard and test preparations was stable for a period of 48hrs

Table 38:Ruggedness- Bench top stability of standard and test preparations

| Time In Days | % Of Standard Preparation | Difference From Initial | %Assay Of Test Preparation | | Difference | |
|---|---|---|---|---|---|---|
| | | | Test-1 | Test-2 | Test-1 | Test-2 |
| Initial | 99.39 | NA | 100.7 | 100.3 | NA | NA |
| 24hrs | 98.65 | 0.74 | 101.9 | 102.69 | 1.2 | 2.39 |
| 48hrs | 99.71 | 0.32 | 98.9 | 98.3 | 1.8 | 2.0 |

8.Robustness:

i) Effect of mobile phase composite variation:

By changing the composition of organic phase from 90% to 110% of organic phase robustness of dissolution method was checked, by injecting the five replicate injections of standard in 90% and 110% of organic phase composition. The system suitability parameter of Metoprolol standard is found within the limits. The method has been found to be robust from the 90% to 110% of organic phase composition in mobile phase.

Table 39:.Robustness-Effect of variation in composition of organic phase in mobile phase

| System suitability parameters | Observed value | | | Acceptance criteria |
|---|---|---|---|---|
| | 90% of method of organic phase | 100% method of organic phase | 110% of method of organic phase | |
| Tailing factor of Metoprolol peak in standard | 1.3 | 1.23 | 1.25 | NMT 2.0 |
| %RSD of standard Metoprolol peak | 0.1 | 0.21 | 0.20 | NMT 2.0 |

ii) Effect of flow rate variation:

Robustness of the method as checked by changing the flow rate from 0.8 ml/min to 1.2 ml/min instead of 1.0 ml/min by injecting the five replicate injections of standard in 0.8 ml/min and 1.2 ml/min flow rate. The system suitability parameter of Metoprolol standard is found within the limits. The method has been found to be robust from the flow rate 0.8 mlto 1.2 ml per min.

Table 40. Robustness- Effect of variation in flow rate

| System suitability parameters | Observed value | | | Acceptances criteria |
|---|---|---|---|---|
| | 0.8 ml/min | 1.0 ml/min | 1.2 ml/min | |
| Tailing factor of Metoprolol peak in standard | 1.3 | 1.25 | 1.31 | NMT 2.0 |
| %RSD of standard Metoprolol peak | 0.2 | 0.1 | 0.3 | NMT2.0 |

iii) Effect of column temperature variation:

Robustness of the method was checked by changing the column temperature at 200c and 300Cinstead of 250C by injecting the six replicate injections of standard at 200C and 300C. The system suitability parameters of metoprolol standard is found within the limits. The method has been found to be robust from the 200C to 300C.

Table 41: Robustness-Effect of variation in column temperature

| **System suitability parameters** | **Observed value** | | | **Acceptances criteria** |
|---|---|---|---|---|
| | **200C** | **250C** | **300C** | |
| Tailing factor of Metoprolol peak in standard | 1.23 | 1.3 | 1.32 | NMT 2.0 |
| %RSD of standard Metoprolol peak | 0.12 | 0.16 | 0.11 | NMT 2.0 |

iv) Effect of buffer:

Robustness of the method was checked by changing the buffer pH from 3.4-3.8 instead of 3.6 by injecting the five replicate injections of standard in 3.4pH and 3.8pH. The system suitability parameters of metoprolol standard is found within the limits. The method has been found to be robust from the buffer pH3.4 to buffer pH 3.8.

Table 42: Robustness – Effect of variation in pH of buffer

| System suitability parameters | Observed value | | | Acceptances criteria |
|---|---|---|---|---|
| | pH3.4 | pH3.6 | pH3.8 | |
| Tailing factor of Metoprolol peak in standard | 1.32 | 1.23 | 1.33 | NMT 2.0 |
| %RSD of standard metoprolol peak | 0.12 | 0.11 | 0.13 | NMT 2.0 |

## 7.8 Stability studies

**Cumulative % release of stability studies of optimized formulation**

Table 43:

| Time (Hr) | Cumulative % drug release | | |
|---|---|---|---|
| | Initial | One month | Two months |
| 1 | 14 | 14 | 14 |
| 4 | 34 | 35 | 37 |
| 20 | 55 | 56 | 57 |
| 24 | 89 | 87 | 85 |

The samples analysed at initial stage and after one month and after two months at accelerated stage.

## Physical evaluation of tablet blend and optimization of stability formulations

Table 44 :

| | **Initial** | **One month** | **Two months** |
|---|---|---|---|
| **Color** | Cream orWhite | Cream or White | Cream or White |
| **Surface** | Smooth | Smooth | Smooth |
| **Thickness** | 4.8-4.9 | 4.8-4.9 | 4.8-4.9 |
| **Hardness** | 8.5-9 | 8.5-9 | 8.5-9 |
| **Assay** | 100.8 | 100.6 | 100.5 |

### 7.9 DISSCUSSION

The IR spectra of the pure drug and mixed drug samples with excipients are shown in Fig 7 to12.

Results obtained from the spectra showed that under stressed conditions the polymers does not influence any interaction with the drug. All the functional groups assigned in the wave numbers in all the different polymer mixtures exhibited maxima which are around the same wavelength and had similar intensities to that of the reference spectrum.

Preformulation studies of drug were performed to characterize the metoprolol succinate. The powder flow properties of metoprolol succinate was studied to evaluate compressibility of the metoprolol succinate, since it has to be formulated as tablet. The results obtained are bulk density 0.328 mg/ ml and tapped density was 0.345mg/ ml and Hausner's ratio 1.05. The results showed that the

compressibility of metoprolol succinate which indicates that the metoprolol succinate has excellent flow properties.

Flow property of drug was good but direct compression method cannot be employed to formulate tablets, because of sticking problem, and also direct compression couldn't retard the drug release because the drug is highly soluble. So wet granulation method was followed.

The drug solution was prepared in 6.8 buffer and scanned using UV-Spectrophotometer in the stage of 400 – 200 nm to determine the λ max. The λ max of metoprolol succinate was found to be at 223 nm. But metoprolol succinate has placebo interaction. So, HPLC method was followed.

Assay method was developed to analyze the content of drug in the tablet. The method was validated through Precision, System suitability, linearity, specificity, precision, accuracy, Linearity of test method, Ruggedness, Robustness.

Accuracy of assay method was established by recovery experiment. Recovery of metoprolol at the concentration range of 25% to 150% was in range of 99.53 – 100.16% which was acceptable.

The precision of an analytical method is usually expressed as the Relative standard deviation (RSD) which should NMT 2%. The RSD of the method was determined to be in the range of 0.3-1.0 which is acceptable.

Specificity was also acceptable as there is negligible interference.

Linearity of metoprolol was taken from standard curve for which the correlation coefficient was 0.9996, which was acceptable. The concentration range for linearity was found between 25% to 150%.

Formulation X-8 was seemed to be close to the innovator's release profile. Then similarity factor was calculated between formulation X-8 and innovator. Similarity factor was 80, so formulation X-8 has similar release profile to the marketed formulation release.

Accelerated stability studies of the optimized formulation were done at $40^0$C and 75% RH for two months. It was seen that physically there was no change

with respect to appearance, hardness, thickness and drug content. The dissolution profiles of one month and two months was similar when compared to dissolution profile at initial stage. This indicate that the formulation was stable at $40^0$C and 75% RH for two months.

The dissolution profiles of optimized formulations were assessed for the release mechanism. The mathematical modelling of the profile into the drug release follows first order release. The value of "n" was 0.68 i.e. it was showing anomalous transport.

Metoprolol succinate was formulated by using direct compression, dry granulation, wet granulation. From all of these only wet granulation process has no tablet sticking problem so this is the preferred method.

It was found that only formulation X8 and X9 were statiscally similar to the marketed product.

X9 was carried out using RMG process which showed sticking problems. Hence formulation X8 was chosen as the best formulation.

Stability studies show that the product is stable under accelerated testing conditions

## 8. CONCLUSION

It may be concluded from the present study that the matrix tablets of metoprolol succinate prepared using xanthan gum and hydroxylpropyl methyl cellulose can be successfully employed as once a day oral drug delivery system.Important formulation factors were systematically studied for the development of modified release tablets of metaprolol succinate. It is possible to fabricate modified release tablets of metoprolol succinate using xanthan gum and hydroxyl propyl methyl cellulose. The combination of matrixing agents namely xanthan gum and HPMC overcomes disadvantages of each polymer. The intial drug burst release was controlled by quick gelation of xanthan gum whereas subsequent drug release and matrix integrity were maintained by firm gel of HPMC. The economy of xanthan gum may help the formulator to decrease the cost of the fabricated product

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